VOLUME 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. PUBLIC HEALTH SERVICE

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

THIRTY-THIRD MEETING

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The above-mentioned meeting was held on Wednesday, January 9, 2008, commencing at 9:00 a.m., at the The Westin Washington, D.C. City Center, 1400 M Street, NW, Washington, D.C. 20005, before Robert A. Shocket, a Notary Public.

REPORTED BY: Robert A. Shocket

COMMITTEE/PANEL:

ARTHUR W. BRACEY, M.D., Chair
RICHARD BENJAMIN, M.B.
ANNE MARIE BENZINGER
JULIE BIRKOFER
JAMES BOWMAN, III, M.D.
JAMES BURDICK, M.D.
WILLIAM DUFFELL, JR. Ph.D.
JAY S. EPSTEIN, M.D.
ANNE MARIE FINLEY
JERRY A. HOLMBERG, Ph.D.
HARVEY KLEIN, M.D.
PETER KOUIDES,M.D.
MATTHEW J. KUEHNERT, M.D.
CDR. MICHAEL LIBBY
DAVID MATYAS, J.D.
GLENN RAMSEY, M.D.
S. GERALD SANDLER, M.D.
DARRELL J. TRIULZI
CELIA WITTEN, M.D.

PRESENTERS:

HARVEY ALTER, M.D., National Institutes of Health

DAVID ASHER, MD, CBER FDA

CELSO BIANCO, M.D., America's Blood Centers

MARK BRECHER, M.D., University of North Carolina Hosp.

JOHN CHAPMAN, Ph.D., ThermoGenesis Corp.

PAUL D. CUMMING, MBA, Ph.D, Talisman Ltd

ROGER DODD, Ph.D., American Red Cross

DAVID LEIBY, Ph.D., American Red Cross

BRIAN McDONOUGH, Ortho Clinical Diagnostics

MARC J. ROBERTS, Ph.D., Harvard School of Public Health

MARTIN RUTA, Ph.D., J.D., CBER, FDA

DON WRIGHT, M.D., MPH, Acting Assistant Secretary of Health

P-R-O-C-E-E-D-I-N-G-S

DR. BRACEY: Good morning, ladies and gentlemen. Best wishes for a healthy new year and welcome to the Thirty-Third Meeting of the HHS Advisory Committee on Blood Safety and Availability. Let me remind all that this Committee is composed in a manner to allow input from diverse perspectives regarding blood safety and availability. We have representatives for patients needing blood products and their derivatives, prescribing physicians, blood procurers and government agencies. Our role is to advise the Assistant Secretary on matters pertinent to developing and maintaining the highest degree of safety possible for these precious blood components and tissues.

At our last meeting we made recommendations regarding coverage and thus availability of erythroid-stimulating agents to the Assistant Secretary. This generated correspondence from the ASH to CMS specifying our position. CMS appreciated the input from the Committee and continues to monitor the ESA situation.

It is interesting to note that FDA is also reviewing additional data regarding the use of ESAs. The need for increasing our ability to assess blood inventory on a static and emergent basis is also recognized as important endeavors by the Assistant Secretary. The Biomedical Advanced Research Development Authority, known as BARDA, is currently modelling blood needs for disaster response. The need for increased participation and basis was acknowledged in Committee recommendations forwarded to the Assistant Secretary for Preparedness and Response. Your efforts are vital in keeping us on track with our primary charge, enhancing blood and tissue safety. Today in a follow-on to earlier Committee discussions regarding a departmental strategic plan for blood and tissue safety, we're here on the potential role of pathogen inactivation in blood therapy.

While we strive to develop surveillance systems that can mentally detect new threats, the lag between detection and action continues to place recipients at risk. There is, however, concern related

to observed and theoretical risks associated with blood modification. We have developed a series of questions focused on this new risk-benefit assessment for the Committee's deliberations. And can we put those questions up to frame the context of the meeting today?

The first is understanding the advances and the challenges facing transfusion safety. What are the major safety concerns? The second is, how would the Advisory Committee prioritize these safety concerns? The third question is, what are the barriers preventing the advancement of technologies or procedures to address these concerns? Fourth question is, what are suggested strategies to address these concerns? And fifth, based on current or potential safety gaps of pathogen test screen development, how would pathogen reduction technologies mitigate or reduce the gaps? And, last, can any of these safety gaps also be implicated into tissue or organ transplantation? That is, are there solutions that may have a commonality between the two endeavors?

With that, I would like to turn it over to

Dr. Holmberg to address introduction of new members and other items of business.

DR. HOLMBERG: Thank you, Dr. Bracey. First of all, let me welcome you to Washington, D.C., and that this is sort of a typical, or atypical, I should say, time of the year here. Usually we're either freezing or under a couple inches of snow and we would also hesitate to schedule a meeting in January not knowing what the weather is going to be like but as you saw the last couple days the temperatures have been very warm throughout the East Coast and produced quite an overwhelming response in New Hampshire yesterday, so, more to come on that.

But, at any rate, I do want to welcome you here and a happy new year. We have a lot of challenges ahead of us in the next year and I really think that the topic that we will be discussing is very important.

I also would like to make an administrative clarification. Many of the members have been called back to serve on this Committee for this session. Actually, Dr. Sandler thought that he just got left

onto the roster there but we did intentionally bring him back again, although this is his last session with us and more to come on that later in the meeting. But, because the nomination process was slow to go through the administrative hurdles, we were not able to name the new Committee members in sufficient time for this meeting and so we do have the prerogative under the charter to extend people up to 180 days to serve on the Committee.

One of the new members, though, that we do have with us today -- and I did get special dispensation to go ahead and enable him to be seated at the table and as a voting member is Dr. Richard Benjamin from the American Red Cross. Welcome, Richard. Dr. Benjamin is completing the term of service left by Mr. Jack McGuire from the American Red Cross so Dr. Benjamin is representing the American Red Cross as a representative member. Since, it is a representative member and not a special government employee, we are permitted to seat him to represent the American Red Cross.

As we go through the roll call today, I would like to also give the Committee members an opportunity to mention any conflict of interest that they may have in some of the topics that we will be discussing today. As you know, we try very diligently to be open, transparent, and to let the Committee members and those people that are speaking and listening know any of the potential conflicts. As you well know, in both the transfusion and the transplantation community, it's a small world and so that there are many people that are interacting and have different conflicts of interest.

As special government employees, all special government employees, and also us as government employees are required to complete a form, what we call Form 450, which is a financial disclosure and we are required on an annual basis to have that reviewed and, any conflict of interest, we have to either be removed from that area or we have to declare it under a waiver.

I realize that in today's discussion there will be a lot of areas where there may be conflict of

interest. I would like, as we go through the roll call, to have the Committee members mention if there are any conflicts of interest, and then I would also encourage any of the speakers and also any individual speaking from the mike to also mention conflict of interests that they might have or association that they may have with any specific vendor. Failure to do so will not permit somebody from the open mike to speak; however, we feel that it is very much part of our transparent society to do that. Okay? So, let me go on through the roll call today. Dr. Bracey?

DR. BRACEY: Present.

DR. HOLMBERG: Dr. Benjamin?

DR. BNEJAMIN: Present. And I should mention a conflict. Clearly I stood on scientific advisory boards for Immuco and for Cerus Corporation.

DR. HOLMBERG: So noted. Ms. Benzinger?

MS. BENZINGER: Present.

DR. HOLMBERG: Ms. Birkofer?

MS. BIRKOFER: Present, and, Dr. Holmberg, I would like to note that on the discussion tomorrow,

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January 10, with regard to Octapharma, Octapharma is a member of the trade association I'm employed by, the Plasma Protein Therapeutics Association.

DR. HOLMBERG: So noted. Doctor Bloche?

(No affirmative response)

DR. HOLMBERG: Dr. Duffell?

DR. DUFFELL: Present. And I wish to note for the record that there could be a perceived conflict of interest. Three and a half years ago I did work for BCT involved in pathogen reduction technology.

DR. HOLMBERG: So noted. Ms. Finley?

MS. FINLEY: Present.

DR. HOLMBERG: Dr. Kouides?

DR. KOUIDES: Present. I should note that I serve on the scientific advisory boards, at present, I serve on the advisory boards for the CSL Behring and Baxter Corporation.

DR. HOLMBERG: So noted. Dr. Lopez-Plaza is not able to join us today but she will be joining us tomorrow. Mr. Matyas?

MR. MATYAS: Present.

DR. HOLMBERG: Dr. Pierce?

(No affirmative response)

DR. HOLMBERG: Dr. Ramsey?

DR. RAMSEY: Present. I also want to note that Octapharma is conducting a trial of a product involving colleagues at my institution, Northwestern

University, and the blood bank has been provided certain logistical support for that trial.

DR. HOLMBERG: So noted. Dr. Roseff is not able to join us today. Dr. Sandler?

DR. SANDLER: Present, and like Dr. Ramsey, our blood bank has Uniplas to be distributed. I have no personal financial interest in the product or manufacturer.

DR. HOLMBERG: Thank you. So noted. Ms. Thomas-Wade will not be with us today. She is ill and we send her our best. Dr. Triulzi?

DR. TRIULZI: Present. And I serve on the medical advisory board for Cerus and was the medical director of one of the trial sites for the Sprint trial, our Cerus platelet product.

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DR. HOLMBERG: So noted. Dr. Kuehnert?

DR. KUEHNERT: Here.

DR. HOLMBERG: Dr. Epstein?

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Klein?

DR. KLEIN: Here.

DR. HOLMBERG: Commander Libby?

CDR. LIBBY: Present.

DR. HOLMBERG: Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Dr. St. Martin? Do we have a substitute from FDA?

DR. WITTEN: I'm here although I'm not formally designate.

DR. HOLMBERG: Oh, okay. Would you like to sit at the table, Dr. Witten?

DR. WITTEN: Okay. Yes.

DR. HOLMBERG: Celia Witten, and also we have in place of Dr. Rios, we have Dr. Burdick.

DR. BURDICK: Present.

DR. HOLMBERG: As I mentioned before, these

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last individuals that are replacing other individuals are representing the government and they are nonvoting members. The only thing, that I would recommend that especially the voting members, as we have discussions if it's an area that you personally are involved with and you have any conflicts, come up for discussion, and you want to say something, I would suggest that you preface what you say with your disclosure once again and also at the time of voting if you feel that there is a conflict, then I would also suggest that you vote accordingly. Okay. Dr. Bracey?

DR. BRACEY: Okay. With that then we will move on with our preparations. The first presentation for this morning will be Dr. Martin Ruta. Dr. Ruta serves as the regulatory counsel in the Office of Blood Research and Review at FDA. He has been working in the Office of Blood Research and Review for 20 years now. He received his Ph.D. in Biochemistry from Oregon Health Sciences Center, his jurisdoctorate from Washington College of Law. The presentation will be an update for the Committee on requirements for human

blood and blood components intended for transfusion or for further manufacturing use, the proposed rule. Dr. Ruta?

DR. RUTA: Dr. Bracey, good morning. Thank you very much and thank you and members of the Committee for giving me the time to update the Committee on --

DR. HOLMBERG: Excuse me, just a minute. We're having a little difficulty with the microphones. Just an administrative word here, when you are finished speaking, if you can turn your microphone off. When you do speak, push the button to get the red light on and make sure that you speak directly into the microphone so that we can capture the conversation. Thank you.

DR. RUTA: Thank you, Jerry. Can you hear me?

DR. HOLMBERG: Yes.

DR. RUTA: Great. All right. So, Dr. Bracey, members of the Committee, good morning. Thank you for the opportunity to present this morning an update on this new proposed rule that published in November. The comment period for the rule is open. You can submit electronic comment to the FDA or written comments. Just for a note, I've given you the Web site for which electronic comments can be submitted. One of the other Web sites in the FR notice actually is not working so if you could use this one if you want to submit electronic comments, that would work out better. If you want to submit written comments, you can submit it to, as listed below following the directions and if you get lost, Brenda Friend is the contact for trying to get the comments submitted.

So, so far we received comments from AABB, America's Blood Centers, New York Blood Center, American Red Cross, Plasma Protein Therapeutics Association, that they have established working groups, addressed many of these issues raised in the rule and they are committed to working with FDA on matters of donor and patient safety and asked for an extension of the comment period. And what I can tell you at this time is that the FDA is seriously considering extending the comment period. I think it's pretty reasonable. It was a long time in the making and we would like to see comments from all of the affected organizations and groups.

So, with that I'm going to try and go through the rule. In trying to put this together, I realize this is probably a one-hour talk and you're going to get about 15 minutes of it, so, I have had to select items and I have had to abbreviate items and I do appreciate the time that I have been given.

So, what are we doing and why? This is a proposal to revise and update existing regulations under the blood action plan and it's to be consistent with current industry practices and put recommendations into regulations. And it's based on comments from IOM, GAO, previous comments, workshops, congressional committees, and even the Advisory Committee on Blood Safety and Availability. And, so, again, as I said, I'm only going to present selected parts of the rule because of time constraints.

So, the proposed rule applies to

establishments that collect and process blood and blood components and it requires the establishment to do, among other things, determine the donor is eligible, and you do that by determine the donor is in good health at the time of donation and does not have factors that can adversely affect the safety, purity or potency of the blood.

And you test the donations for -- there's a new term of art, RTTI, which stands for relevant transfusion-transmitted infection. I will be going over that shortly. You would determine the donation is suitable and if the donor does not meet eligibility criteria, you would determine the donor is ineligible, defer the donor and notify them. There's also a permissive part of the regulation that allows for, does not require requalification of deferred donors.

Okay. So, I want to go over a new term of art, which is relevant transfusion-transmitted infection because it turns up in a couple parts of the regulation. And, so, as you can see here, as I'll show you, it's a two-part definition. Part one is a list of specific agents, and these should all be familiar to you, HIV 1 and 2, hepatitis viruses, HTLV I and II, syphilis, Creutzfeldt variant, Creutzfeldt and malaria. So, if the agent made this list, then we currently have a recommendation, requirement for donor screening or for testing. And I've indicated with an asterisk where there's a requirement for testing.

Now, as with any list of agents, it's going to get out of date with time. And one can look at that list and say why isn't, you know, West Nile or other agents included in it. So, we've tried to construct provisions that would provide some flexibility for indicating when a new agent that comes along would also be a, considered a relevant transfusion-transmitted infection. And I have had to condense two parts of the regs here and this would be another agent, not on the list, that causes significant health risk and here we're talking about fatality or hospitalization for which there may be a risk of transmission by blood or blood products. Those two bullets are actually what a transfusion-transmitted infection is. To be a relevant infection it would have to have appropriate screening measures are developed and/or a screening test is licensed or approved and have sufficient incidence and/or prevalence to affect the potential donor population, or -- and this is a new provision -- may have accidentally or intentionally been released in a manner that could place donors at risk of infection. What we have in mind here are the bioterrorist events, that's the anthrax exposures that, you know, came about in 2001.

So, if an agent would make it to the point where we would consider it an RTTI, we would envision that we would have public discussion and issue a guidance document and then we would say in the guidance document we think you need to screen, we think you need to -- and I'll go through it as we continue through the rule.

So, one of the provisions I wanted to go through is educational material. So, we have been recommending HIV education materials since I think

1992, at least. This is actually a new requirement.

It would be a new requirement in the reg that's finalized this way. And, again, remember, this is a proposed rule; it's not the final rule. So, we would propose to include that there be a requirement that educational material be provided to the donor about relevant transfusion-transmitted infections.

The educational material would contain relation between behavior and the disease agent, signs and symptoms, and instruct the donor to self-defer. And we're seeking comments in this provision and many other provisions within the proposed rule. For here we're seeking comments on how comprehensive the material should be and what format. And I think hopefully it's not too unfamiliar to you because educational material I think is included in, you know, as a common practice within, for example, UBHQ.

So, now I'm going to go into donor eligibility. How do you determine donor eligibility?

The first two bullets, one and two, really apply to returning donors and you would assess the deferral status of the repeat donor prior to collection and you

would assure that the donation interval is appropriate. So how would you do that? Well, I'll show you in a minute. And, you would also assess the medical history of the donor and perform a limited physical assessment. And in assessing the medical history, one way it could be done is through a questionnaire.

All right. So deferral status, this is a new proposed requirement and it would propose that all facilities under a single license share a common list of donors who are deferred to prevent collection and distribution of unsuitable units. And these are for certain types of deferrals and I'll try and point them out to you as we go along. They're usually related to risk of disease transmission. And, here we're seeking comments on what information should be included in the deferral registry, is it technically feasible to do this, is it feasible to have a national donor deferral registry, such as exists for source plasma, and we have a number of questions related to patient and record confidentiality and you can see them listed here.

All right. So, how would you assess risk

factors for a relevant transfusion-transmitted agent? And we have a list here. There's a new term of art again, social behaviors. By that we mean terms such as IV drug use, exchanging sex for money or drugs or MSM behavior. And, then it would also include medical treatments or procedures associated with a relevant transfusion-transmitted infection, for example, dura mater grafts, or transfusions, signs and symptoms of a relevant transfusion transmitted infection, incarceration in a correctional institution, number four, and intimate contact with an individual who is at increased risk for exposure or infected with an RTTI. By that we mean, for example, a heterosexual partner of an IV drug user. And, finally, an exposure of nonsterile percutaneous inoculation. So, these six we are proposing would get you onto the deferral list that would be shared among the different establishments.

Okay. There are other factors that we think should be assessed for and these are signs and symptoms of a recent illness, for example, a recent medical or dental procedure. Medication, this is again

new to the regs but a long-standing practice, and it would put into the regs a requirement that you defer donors for exposure to certain medications that can affect the blood or blood product. Major surgical procedure, what we have in mind here are actually a surgical procedure within the past 12 months and it's intended to protect the health of the donor. The rest, I think, travel to or residence in an area endemic for a relevant infection, i think that's self-explanatory. Xenotransplantation, exposure or possible release of a disease agent in number six is a result of the anthrax exposures.

So, again on this list, one through six we're proposing would make it to the list of shared deferral criteria. What's also new that we're proposing is the deferral for pregnancy, at the time of six weeks before donation -- may be a common practice but it's new to the regs -- and, finally, unreliable answers to medical history questions due to the apparent influence of drugs, alcohol, et cetera. And this has actually been in the source plasma regs for

several decades. It's actually new to the whole blood. So, one of the things we've done here is to try and combine the donor suitability criteria for source plasma and whole blood into one section.

Physical assessment, so, we would recommend that a limited physical assessment be performed to determine that the donor is in good health. And the current regs require that the donor's temperature be normal. Here we're proposing a definition of what normal would be. The current regs also require that the donor have a normal blood pressure but here we're proposing upper and lower limits to blood pressure and we're asking comments from the industry on the need for these limits, if there are any adverse events associated with donation by someone because of, you know, high or low blood pressure, the accuracy and ability to measure, you know, the systolic and diastolic blood pressures accurately.

Number three in the codified deals with hemoglobin or hematocrit determination. This is done both as a donor protection and to ensure that the, you

know, blood is potent, has enough red cell cells in it. And currently the regs require that the allogeneic donor have 12.5 grams of hemoglobin per 100 milliliters or hematocrit of 38 percent. What we're asking for are comments on what appropriate levels should be and we are asking whether we should have different levels for female donors as opposed to male donors. This is something that's been talked about for a long time and we've gotten some comments on this provision.

All right. Part two of the physical assessment is that the donor have a normal pulse. This is actually a requirement for source plasma but would be new to the whole blood. The donor weight, and we would propose that the donor weigh a minimum of 110 pounds. For the skin examination, we would continue the requirement that the donor site be free of infection or signs of drug abuse. Okay. So, that takes us through the, briefly through the medical history and physical assessment.

So, I wanted to spend a few minutes talking about testing requirements for relevant

transfusion-transmitted infections. So, the current test regulations -- and this is a very abbreviated combined slide, so, sorry about that. In the interest of time I've tried to consolidate things. But it would require that donations be tested for relevant transfusion-transmitted infections and that would include retaining the requirements for HIV-1, HIV-2, HBV, HCV; HTLV, source plasma, we don't have a requirement for HTLV testing.

And for syphilis we're again calling on whether there's data on the need for continuing syphilis testing. This issue arises periodically. We addressed the issue seven years ago with the Blood Products Advisory Committee and at that point they felt there wasn't sufficient data to discontinue syphilis testing. We're again asking, we're revisiting the issue.

Then the test reg is modified to say that there would also be a requirement to test for other relevant transfusion-transmitted infections. So, there would be a new agent, the agent would meet the criteria

in the slide they showed before, there would be a screening test that's been approved. Then there would have to be a scientific determination that testing is needed. We generally do this through a public process, and typically we would go to the Blood Products Advisory Committee and ask whether the data supports a recommendation for screening with this, you know, for this new agent, with this test that's been approved.

And we would then issue a guidance document saying that here's this agent, a new test has been approved, we think that you should test for this agent under this reg and we would seek public comment.

We're also making some slight modifications to the requirement for supplemental testing. So, as you remember, if a donor tests reactive on the screening test, that we require that a supplemental test be performed. And, the proposed change that we're making here is that the establishment use a supplemental test or other appropriate test, and what we're allowing for here is the use of multiple screening tests to confirm the infection or provide

additional information about the presence of the analyte.

This came up a couple of years ago when we were approached by blood establishments asking about the continuing need for Western Blot testing, if the donor tested reactive on the HIV, EIA, and also reactive on the NAT test. And, we took that to the Blood Products Advisory Committee and set up a PHS working group and concluded that if both the EIA-indicating antibodies were present and the NAT test indicating the virus present both were positive, that that was sufficient to indicate the person was infected and that there wasn't a need to perform the Western Blot.

So, we're trying to provide flexibility to allow for other situations that might arise. Still, I think supplemental testing is important and we're not trying to discourage, you know, supplemental testing and do appreciate it when manufacturers come forward with those kind of tests.

Okay. The proposed regulation would also

contain a requirement for testing of platelets for bacterial contamination prior to release. And we're asking whether there should be speciation of the bacterial contamination and should we require donor deferral and notification if the bacteria that's identified indicates an endogenous bacteremia. And, finally, is there a need for testing of other types of blood components?

So, I've skipped over -- no, I'll come to it later. Okay. So, I'm getting toward the end only because I'm trying to keep to my time limits. And, finally, after going through the determination that the donor is eligible and that the donation tests negative, you would determine that the donation is suitable and that would include a determination that the donor is not currently deferred from donation, that the physical history that was performed indicates that the donor is in good health, that he doesn't have risk factors that we just went through, and that the donor's blood tests negative for the infectious diseases that we just went through, and for platelet components, that donation

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tests negative and, finally, I have to leave it with the donation meets the other requirements in this subchapter.

There are many other requirements that we are proposing to change that I don't have time to present in this limited talk but I do want to mention a few of them, if that's okay, and you can take out the hook whenever you want me to stop talking. But, there are a number of other provisions within the rule that we're proposing and there are some changes in medical supervision, including use of physician substitutes.

There's a new provision on a donor's written statement of understanding that would include that the donor reviewed the educational material, that they won't donate if they're at risk, that they agree to testing, including supplemental testing, and they understand they will be deferred if needed and they understand the risks of the donation process.

In addition, we have specific requirements for whole blood related to donation frequency. We have modifications to the labelling requirements for

therapeutic phlebotomies for hereditary hemochromatosis, that it doesn't need to have the disease stated on the label if the donor otherwise meets the eligibility criteria and there's no charge for the phlebotomy. That actually was a recommendation of this Committee many years ago. We also have additional specific requirements for plasma apheresis and for source plasma but in the interests of time I'm going to stop here. And I thank you, Dr. Bracey, and members of the Committee, for the opportunity to present and we're asking everybody to please submit your comments to the docket and we'd really appreciate if you could submit data along with the comments.

DR. BRACEY: Thank you, Dr. Ruta. Questions or comments from the Committee on this presentation?

MS. BIRKOFER: I do.

DR. BRACEY: Yes, Ms. Birkofer?

MS. BIRKOFER: Thanks, Dr. Bracey. Dr. Ruta, I really appreciated your overview of this comprehensive proposed rule and, as you noted, not only is it comprehensive but it's also reliant upon you receiving good data to the docket. And I just wanted to share with the Committee that the PPTA takes this very seriously and, as you know, we are working with the AABB in a working group to address the many issues in this proposed rule.

But, I just wanted to make sure the Committee understood, PPTA respects, of course, the FDA's process but we are requesting that an additional six months' extension be put in place that would allow time for an adequate review and response to the proposed changes to the regs as well as our ability to compile and review the significant amount of data that is required for the FDA to move forward. So, we do appreciate your consideration of an extension but I wanted to just provide the Committee that, why we're requesting six months and how important that is. So, thank you.

DR. RUTA: Yeah, thanks. We've kind of heard that from everybody and we appreciate the comment and I think it's going to be helpful to get data from everybody, so, please continue working on gathering the data.

DR. BRACEY: One question. Could you restate the deadline for comments?

DR. RUTA: The first deadline was 90 days, February 6, and we've been asked for extension for the deadline and I think that's reasonable.

DR. BRACEY: And one thing that I would note is that in our earlier meetings in discussing a strategic plan, the notion of a national deferral registry was considered to be something that would be important in terms of protecting or improving the safety of the blood supply so we certainly hope that you can do something to stimulate that effort.

DR. RUTA: Thank you very much.

DR. BRACEY: Additional questions? Dr. Kuehnert?

DR. KUEHNERT: Hi. I just, I wondered if you could just briefly describe how, what the process was for what organisms are on the list. And, particularly, since there are some organisms that are aren't screened from a laboratory standpoint, so, I just wondered, is there some significance to those organisms versus those that are on your next slide about other relevant infections as far as how they're going to be handled in this proposed reg?

DR. RUTA: There are actually a couple questions there, Matt. Thank you. So, the list is always time dependent. You know, it's a certain frame of time when we say, you know, this is it, at any given time in the future it will become out of date if there's just a list so that's why we have the second part, to provide flexibility for other agents. For all of the ones that are currently listed there, there is currently some type of requirement for screening or for testing, you know, in place.

So, that's one of the reasons that they're there. How they would fit in, into the regs, I can go over that again, and that is that we're proposing educational material be provided as one place for relevant agents, so, for example, we would say you need to have educational material for these, you know, agents and presumably that's something that we might work with, you know, CDC on and with other groups as well, educational material. We would come up with donor screening agents, and typically, a new agent comes along, agent X, and we realize this may be a threat to the blood supply; typically there's no tests available. The first thing you can do is come up with screening criteria to try and keep out at-risk donors. And down the line if a test is developed, then you can think about is it necessary to have the test in place. So, there are independent judgments of whether screening should be done for this agent and then whether testing should be done for this agent.

DR. KUEHNERT: Okay. That's very helpful. I just wondered, just a thought that babesia is not on the list, and they ought ask the question, you know.

DR. RUTA: Sure. Proposed rule, you know, we'll take comments. Okay?

DR. KUEHNERT: Okay. Thanks.

DR. BRACEY: In the interests of time we should move onto the next speaker -- Ms. Finley?

MS. FINLEY: Thank you very much. I'm sorry. Dr. Ruta, I just had a quick question. First of all, I wanted to commend the agency. I know this was a lot of work. It took many years of development. So, it's wonderful that it's now out there for us to comment on.

Secondly, I wanted to ask what the extension, the six-month extension would take it from February 6 out six months, but then does the agency have some flexibility regarding implementation of the final rule, and the period for that, and would they, would the agency consider tightening up the final rule comment period or the period of time it would take for the final rule to be effective?

DR. RUTA: Regarding the extension timeframe --

MS. FINLEY: Yes.

DR. RUTA: -- we would ask for six months' extension. I think it's reasonable. It's kind of over my head to grant it. You know, there's a process within FDA that it has to go through. I think it's not

unreasonable and we do want the data from all the affected parties, so, you know, I certainly hope we get that. Second, as far as how long will it take to finalize the rule, gee, I don't know that. You know, there are a lot of different parts to this.

MS. FINLEY: Yes.

DR. RUTA: And again, we have to go through the procedures, the administrative procedures, and there are other factors that come into play. And we can think about how to finalize it after we get the comments and then figure out what the final rule should be --

MS. FINLEY: I think on behalf of the patient organizations there has been a long history in the past, not necessarily recently, of very extensive comment periods followed by extensive periods and I just think the agency has really made a very concerted effort to try and bring this to a close. I have no problems with the six-month extension on the comments if that's what we need to get it right but I just wanted to express the opinion that it is important to

bring this to a close. I'm sure you're just as anxious as everyone else to do so.

I had one other question and a clarification and I'm sure I'm not the only person in the audience that wondered, with regard to implementation of testing requirements, am I reading this correctly that if there is a screening test licensed, approved, or cleared, for anything that's considered to be an RTTI, then it is expected that it would be implemented by the collection organizations?

DR. RUTA: Not exactly.

MS. FINLEY: Okay.

DR. RUTA: What would happen at that point is a test would be approved for this new agent and then typically there's a public discussion.

MS. FINLEY: Yes.

DR. RUTA: Like a BPAC discussion saying

here's a new test for this agent, do you, you know, does the Advisory Committee agree that the data supports your screening; so, there would be a public processes. It's not an automatic, and there can be

things that are on the list for screening, meaning donor history screening but not make it to the testing part.

MS. FINLEY: Yes.

DR. RUTA: So, it's not an automatic. It's a two-part, you know, discussion and decision. That's the way that we're thinking about it. Again, it's a proposed rule.

MS. FINLEY: Okay. All right. Thank you very much.

DR. RUTA: Thank you.

DR. BRACEY: We need to move on. Thank you. Our next speaker is Dr. Roger Dodd. Dr. Dodd -- and actually, I should mention that Dr. Dodd is coming out of order because we've had some travel problems. But, Dr. Dodd received his BS in biochemistry at the

University of Sheffield. He worked as the Scientific Officer in the Ministry of Defense for the UK and he left to come to the U.S. to work for the Red Cross where he's been employed for the last 36 years. He's been very instrumental in developing a number of assays

and improving our safety with regard to transfusion-transmitted infections. Dr. Dodd has done extensive work in terms of documenting current risk, which has been published in many well-received publications, often quoted in slides we've often seen. He will share with us today residual risk for pathogen transfusion-transmitted disease. Dr. Dodd?

DR. DODD: Thank you very much, Dr. Bracey, members of the Committee. I would like to comment that my establishment does have funding for contract research for Abbott Labs, for Cerus and for Navigant but I am not personally conflicted beyond that.

I was given a very wide remit and I hope that I can satisfy all the questions that Dr. Holmberg fired at me. I think that we all recognize that blood safety is an area of considerable public regulatory and political concern, even though transfusion appears to be one of the safest therapeutic measures available. Surveillance, donor selection, testing and hemovigilance, along with the use of quality systems and deferral registries have led to a situation where

residual risk for key infections may be lower than one in two million units transfused. Nevertheless, further measures are proposed and are vigorously supported by some thought leaders.

Is there a framework for appropriate decision-making or is it appropriate to continue to seek a zero-risk blood supply? Will the current system of healthcare funding support such an approach? I think this is the core issue for me.

So, I'm going to spend a little time talking about residual risk and how it is estimated. These are questions that Jerry asked me to think about. How safe is safe? What are the needs, pathways and barriers? And I will really just make a few introductory comments because I think that really is the charge of this Committee.

There are a number of agents, as you've just heard, for which there are clear, current interventions. In some cases we have donor questions plus testing, hepatitis B, hepatitis C, HIV, HTLV, syphilis. In some cases we have testing really only

although theoretically they're supported by some questions, West Nile virus, T. cruzi and also partial testing currently for CMV and for bacteria.

In other cases we rely only on questions, CJD, variant CJD, hepatitis A virus, malaria, babesia, leishmania. And there are some areas where questions are assumed to have impact but there's no clear evidence of whether they do or not, HHV-8, other tropical infections which are usually thought to be trapped by questions about malaria. And, questions have been used for emergent situations, for example, SARS. These questions are often based on travel or exposure.

Recent additions to the blood safety armamentarium have been the initiation of a more formal approach to hemovigilance in a really private government partnership; approval and limited use of HBV DNA testing; Chagas testing, which was adopted by the majority of blood collectors over the past year, and bacterial testing of platelets by culture and recent approval with rather limited claims for a point-of-use

test and the addition of individual donation testing for West Nile virus.

Why then is there still risk that we need to consider? In some cases it's recognized that there may be a failure of the donor selection process. In some cases, as I've pointed out, we really don't have any tests available or the tests are not adequately sensitive. There has been data indicating lab failures but most tests are backed up with secondary tests. So, this is a very low level of risk. The possibility of mutant or variant organisms which are not the same as the prototype used to construct tests is considered, and, there's some evidence from outside the country that in some cases such variants are not always detected or have not been in the past. And window period infections are still the major source of residual risk and Mike Busch could well speak to this were he invited to do so. This is the period in early infection with a circulating agent but prior to test positivity and we'll talk more about that.

In the past it was possible to measure the

risks of transfusion infection by direct observation. And, there have been a number of well-known and well-cited posttransfusion studies, the TTV, the ongoing NIH study -- and Harvey Alter is in here -- and a specific study, FACTS, was performed on a large number of cardiac surgery patients who received about 100,000, 110,000 units of blood in aggregate. But nowadays most infections are too infrequent to measure this way.

A somewhat similar approach was also undertaken by Mike Busch so many years ago along with Garis Vyas in which there was an heroic attempt to culture seronegative donations for HIV. I think out of a large number of donations one was found to be positive but we now have similar issues. And in the past it was possible to back-calculate risk from historical data but this is now no longer possible.

And here's a slide which is actually quite hard to come by. This is a synopsis of one of Harry Alter's ongoing studies at NIH. And the point that I want to make with this slide is that he no longer is

able to detect any cases of hepatitis in his studied population. The other point is that there's an area of continuous improvement with added activities, donor questioning, and increasingly sensitive tests, has had a tremendous impact on blood safety over the years.

In cases where there is testing it is possible even in the absence of measurable levels of posttransfusion infection to estimate the risk from donor data. And the risk has been defined as a function of the window period -- that is the time when agents are circulating but not detectable -- times the incidence of new infections. And in order to do this of course you need to define the window period and the incidence rate. And one can update these estimates by reference to the impact of new tests on the shortening of the window period.

Incidence rates are regarded as new infections per person, per time. For example, the number of new cases of HIV in 100,000 donors in one year, obviously measured only amongst repeat donors with at least two donations and in our case we used

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within a two-year study period. The numerator is the number of seroconversions and the denominator is the person-years of observation. And here -- and I can hardly see it -- there are some estimates we made a few years ago of incidence measures per hundred thousand person-years in the Red Cross donor population.

And, in general, what we're seeing is between one and two and in the case of HTLV 0.2 new infections per hundred thousand donations per year. This is a tribute to the impact of donor selection and testing. And, you can see that these numbers are quite low and when you realize that the window period is also measured in days, the actual risk comes out to be relatively low. Other methods, though, are necessary to account for incidence in first-time donors and if incidence in first-time donors differs, then the overall risk estimates must be adjusted.

Incidence in first-time donors has been established by the use of a less sensitive test method, pioneered by Mike Busch and Sue Stramer over the years. And, this allows you to determine the proportion of

test-positive samples that are in the early period while the antibody levels are still increasing. This is currently available only for HIV.

Similarly, one can use the results of

nucleic acid testing data from routine HCV testing and from HIV testing because an individual who is NAT-positive alone, is in the case of HCV, in the first 50 or 60 days of infection. So, NAT yield and NAT window period can be used to calculate incidence. And a number of studies have indicated that first-time donors do have a higher incidence level than do repeat donors. The factor for HIV and HCV has generally been found to be somewhere between two and three, which I think represents a lot of social differences among some first-time donors, and we don't have time to go into that.

More recently, using a somewhat different approach to the measurement of incidence, we have found that this 2.4-fold increase, at least among HIV positive donors, may be reflective of infection that occurs quite close to the time of donation and

therefore may be a little bit skewed if you broaden the observation period out a little bit.

Window period in the past was measured actually by observation of infection. Among exposed donors I have determined from lookback studies or determined by direct observation in cases where exposure and outcome were known. But again, Mike Busch pioneered probably a much better way of doing this, which arrives at a similar outcome by back-calculating the linear extension of the ramp-up period of infections. This is basically the level of nucleic acid in the early stages of infection, and back-calculating that to the point at which one would assume the minimal infectious dose was present, in Mike's case usually about one particle, one viral particle or one DNA or RNA molecule in 20 "mils."

And in published studies Mike has dissected the window period into a number of sections. This is the window period, if you will, and this, the residual risk is based on what is not detected by the various methods identified here. So, in most cases with

mini-pool NAT testing we're talking about nine or ten days for HIV and seven or eight days for HCV reduced by approximately a half if one were able to do single donation, nucleic acid testing, which would be quite an effort. And similar data are present for hepatitis B, based on HBsAG. And again there are other ways that suggest that this is quite reasonable.

These data were the last really serious evaluation that we did. I must admit they go back to 2001. I would say in general that since that time we have been seeing the incidence rates of these infections declining in our donor population and some increase in sensitivity. But, what I wanted to point out was that in this case about 1 in every 200,000 donations might be expected to be infectious for hepatitis B among repeat donors and 1 in 144,000 amongst all donors.

If you look at the figures with nucleic acid testing -- this is minipool currently in use -- we see about 1 in 1.4 million for HCV and about 1 in 1.5 million for HIV and 1 in about 2.2 million for HTLV.

This is the anticipated number of viremic donations per given number. And, we would assume that in a worst-case estimate all of those might be infectious.

I would probably ask you to look at this in your own handouts. These are similar data from Mike Busch for HIV and HCV and these are based on the methods that he's pioneered for measuring window period and using existing incidence measures. And they come out remarkably similar. The issue that's a little bit different here is there's a column of figures indicating the anticipated risk if you were able to test every donation by a single nucleic acid test.

Amongst other viruses I don't have well-classified rates here. But, for West Nile virus, for example, there were 23 cases of West Nile virus transfusion-transmission recognized in 2002 and since that time when testing was initiated there have been a total of nine cases but only three of these really have occurred since the use of selective individual donation testing.

So, in general, West Nile virus is tested, RNA is tested in small pools but in epidemic periods and areas we revert to individual donation testing and this is a really a pretty good record. And this is a tremendous example of a reaction to an emergent infection. B19 is another transmissible virus but amongst recipients of whole blood there are really only about four to six cases that are well-documented and few, if any, of these have significant clinical outcomes, a couple of them.

HHV-8, we know that transmissibility has been established outside the U.S., in studies done in Africa. There's also a report that indicates two potential but not confirmed transmissions in the U.S. These occurred quite some years ago in an environment where blood was not leukoreduced.

CMV has an unknown frequency of posttransfusion infection. There may still be an occasional risk, even in the face of leukoreduction and/or testing. And, we know, for example, that Dengue virus has been transmitted. There is one reported event in Hong Kong. There's another one in the literature from Singapore, and this is one that we're keeping our eyes on, hepatitis E virus, hepatitis A virus, and even Colorado Tick Fever virus have been transmitted but only very rarely and not always in the U.S.

Speaking of bacterial testing, bacterial testing of apheresis products was initiated in 2004 and our current assessments of residual risk have been based upon reporting of posttransfusion sepsis. And using similar parameters in a similar hemovigilant system, prior to the initiation of testing in the Red Cross population, we saw septic reactions reported in about 1 in 40,000 apheresis platelets issued and fatalities in about 1 in 240,000.

After the initiation of testing, septic reactions were reduced to 1 in 75,000 with fatalities at 1 in 500,000. And this was published last year by Anne Eder and colleagues from the Red Cross. And further reductions are attributable to the use of sample diversion pouches, which have significantly reduced the number of bacterial sepsis events from skin bacteria.

Some bacteria are infectious by different routes and establish an infection rather than creating a sepsis. Syphilis, of course, is the most well-known case but no recent cases have been reported. And in studies done by Sharon Norton some years ago test-positive units were not found to have detectable T. pallidum DNA or RNA. In the end the total was 169, I believe, in that study. So, there was no evidence even amongst those donations thought most likely to be infectious that there was any replication of T. pallidum.

This is one bacterium that causes -- which one is it, David? Yes, human granulocytic erlichiosis, and, there's one potential transmission that's been reported but has not been written up and this was quite some years ago. And there are a number of other bacteria, including the Lyme disease agent, that may be thought to be transfusion-transmissible but have not been reported in the U.S. in recent years. That is merely one example. So, there is residual risk from bacteria even in the face of testing and we'll probably hear more from Mark on this.

In terms of parasites, currently there's fewer than one case per year of transfusion-transmitted malaria. I would point out in passing that this is at a cost of about 100,000 deferred donors per year, many of whom do not come back again.

Chagas disease, there have been seven known transmissions in the U.S. and Canada, but testing, as I told you earlier, was initiated last year, and the overall seroprevalance rate for this agent is about 1 in 30,000 in the U.S., and the pre-test risk of transmission was probably significantly less than 1 in 300,000. Our current data suggests that fewer than 1 in 10 of potentially infectious donations are associated with a transmission.

Babesia, which has already been mentioned, is a malaria-like parasite that's endemic in particularly northeast coastal areas of the U.S. and the upper midwest. And to date about 60 cases have been reported in the past 20 years or so, and risk has

been definitively shown to be as high as 1 in 1,000 in areas of high endemicity. And at this time there is really no effective intervention. We do ask donors if they've had babesiosis but this is not a very useful test.

So, what do we see in reality, which is really the question, how many actual cases get reported or identified? For HIV there have been four or so transmissions since testing was initiated but we have not seen any transmissions since 2002. HCV, no transmissions reported since 1999. Hepatitis B, fewer than ten transmissions reported in the past four years and none after the implementation of the more recently licensed, highly sensitive HBsAG tests. HTLV, there has been to my knowledge no transmission reported really since we initiated testing. There were certainly lookback cases that were identified, so, that's back in the eighties. West Nile virus I already mentioned and malaria and babesia.

I just wanted to add at the bottom, although this is neither a virus or bacterium or a

parasite, that there have been no cases of CJD itself reported as transfusion-transmitted anywhere in the world but there have been three clinical cases and one known nontransmission of the agent for variant CJD in the UK. These differences in our studies turn out to be significantly different statistically and certainly, looking at CJD if infectious at all by transfusion, is very much less so in variant CJD. Note that almost all of this really depends on reporting and some of it is supported by the fact that lookback really picks up cases so where there's no lookback, the efficacy of the reporting is probably not so good.

Emerging infections, I think we'll hear a lot about it, and, as we all know, emerging infections result from new agents, from agents that are expanding their range, those that are imported, those that are re-emergent as a result of generally environmental change, those that are newly recognized but been with us for a long time, and those that really become a problem as we engage in more aggressive patient treatment.

And, I think that we do need to keep up an emerging infections program. I won't spend very much time on it other than to point out that there are two axes of concern. There's a public health axis, how many damage will this agent cause, and there's a public and political concern axis, which is not necessarily related, which is how much are people concerned about this.

It's inherently difficult to define the risk for an infectious agent even though some may show very rapid progression and expansion, some of which is not always predictable as, for example, the appearance of chikungunya, not so much in the Indian Ocean but recently in Italy. The precautionary principle is often invoked for emerging infections but often without benefit of the moderating commentaries that come along with the precautionary principle, and unique solutions may be needed because there really is no unifying epidemiologic patent for these emerging infections.

So, a few words about these surrounding issues. How safe is safe is again a question that's

very hard to answer because the perception of risk among the population is not straightforward, very low risk values are hard to conceptualize or visualize. Somebody once said to me, well, a 1 in 50,000 risk is like taking somebody out of the audience in a ballpark and shooting him on the spot. Well, that does give you a -- not really the sort of thing that we want to deal with but that does give you a chilling thought of what is 1 in 50,000.

People don't ever equate voluntary risk, that is, risk that they undertake on their own with imposed risk, that which is out of their control, and fear and dread have a major impact on perception. And it seems to me that medically speaking a diffuse risk such as a drug reaction seems to be more palatable than a focused risk, such as, this unit was infectious, why couldn't they have dealt with it.

One way of looking at risk and thinking about risk is this Paling scale, which is a log scale and right in the middle is a risk of one in a million which is generally thought to be relatively innocuous,

and, as pointed out here, is said to be the USA/FDA point below which any risk from a food additive is considered too small to be of concern. That's down here.

And most of the other everyday risks are much greater than that. If you take a look -- and it's not easy to find these things for public presentation -- if you look at some of the transfusion risks that are noninfectious, they do in fact all fall in this 1 in 1,000 to perhaps 1 in 300,000. Most of the infectious risks that I have discussed with you fall very much on this side of the line.

So, the infectious risks as we now know them really fall on very much the lower side of the general risk equation. In fact, reported deaths from transfusion amount to fewer than 50 reported cases per year, a minor proportion of which are from viral infections, while the risk of death from hospital errors has been estimated on the order of 100,000 per year. But transfusion medicine represents only about 2 percent of healthcare expenditures. Very crude and

probably completely inappropriate math suggests that blood transfusions are way ahead of everything else in this context.

The drivers of safety we're going to hear about. There are ethical imperatives, advocacy, accreditation issues can drive safety, public and political pressure, competition, I think in our environment, what other countries are doing, what technologies are available, fear of litigation, unfortunately, and, as you heard from Martin, regulation.

So, what are the needs within which we operate? Are we looking for zero risk, all the safety we can afford, acceptable risk, an arbitrary value such as the one that was cited for food additives, risk that's as low as reasonably achievable or continuous improvement with no specific target, are there are there different standards for different agents, think about HIV and variant CJD as compared to, say, babesia, and can we moderate the escalation of current interventions involved in deferrals in testing?

Well, I think that what we're really working at, at the moment -- I don't know if this is the right answer, this does seem to be the answer -- in our environment, is that we are looking for risk to be as low as reasonably achievable, if we know what "reasonably" is, and/or continuous improvement with no specific target.

The pathways to deal with this, education and advocacy, this perhaps can deal with what is reasonable, a rational public health decision structure with an explicit balance of costs and benefits across healthcare. And I don't like to say this after Martin just got up and said, okay, the FDA will look after this, we'll decide when a transfusion-transmissible infection becomes a relevant transfusion-transmissible infection.

We need to think about how we pay for inherent safety because this is very difficult in this country and other pathways to achieve more safety or more tests or better tests or less use of traditional blood or inactivation and removal, which is part of the

component of this meeting.

We know that there are advantages and disadvantages of pathogen reduction, which will be talked about in great depth, but there are barriers. I think the decision structure or the indecision structure is very difficult to deal with in the U.S., with an absence of a consistent coherent approach there are really no models to deal with blood safety. The available providers of technology are getting a shrinking interest in this field and you will hear from Brian McDonough about this.

Available resources, do the economics of healthcare favor adoption of safety measures in the absence of regulatory requirements or cost savings? Are there competing priorities? There certainly are for the industry that supports us. Are there limitations to technology? Yes, indeed. And the regulatory environment does in fact make the requirement for approval hard to meet and outcomes of approval can be restrictive.

So very, very briefly, infectious outcomes

of transfusion are reduced to between 0.2 and 5 per million units for agents of major concern. Other infections are generally occurring at a rate on the order of one or fewer cases per year in the U.S. currently. Further reductions could be achievable by extensions of current testing approaches, the perceived need for further improvements and for a means to combat emerging infections certainly exists and will continue to exist.

We are currently facing an expanding number and intensity of interventions and a lack of clarity on decision processes for further safety improvement. There is also a lack of clarity on market prospects for further safety improvement unless there's some measure to drive these into place. And to me the current pathways are unclear and may be much more so for tissues and organs. Thank you very much.

DR. BRACEY: Thank you, Dr. Dodd, for that comprehensive and thoughtful review. Questions and comments for Dr. Dodd? Dr. Kouides?

DR. KOUIDES: Dr. Dodd, thank you. I had a

question when you had mentioned that there haven't been any cases of hepatitis C since '99 and HIV in 2002 and yet based on the numbers of the donor risk, in this, is it that this is underreporting or is it that the transmission is naturally a hundred percent and does that mean there are other host factors or other issues that perhaps mitigates the true infectivity and does that, you know, how does that factor in?

DR. DODD: Yeah, I think that's a wonderful question. I think the real answer is it's a little of both. I think that there certainly is underreporting. It would be foolish to accept what we don't see as being the truth. Everybody knows that. And, given that oftentimes the way we pick these infections up is because we find we have a donor who has just seroconverted and therefore may previously have given an infectious donation, we then go find the recipients and lo and behold perhaps one of them has been infected or some of them have been infected.

If you have a first-time donor you don't have that privilege so you will never see that kind of

infection associated with a first-time donor, which probably offers 30 to 40 percent of the overall total risk. So, that is one issue where you don't find it if the infection doesn't appear as a clinical case. I think that once you get to these very low potential levels of contamination that you calculate your risk from, not in all cases will there be an infection and this is particularly the case with some of the other infections. So, yes, all of the above is really the answer to your question.

DR. BRACEY: Dr. Benjamin?

DR. BENJAMIN: Thank you. I just wanted to make a comment and update Dr. Dodd's data on bacterial contamination, the most recent data from the Red Cross concerning reported septic reactions. There's about 1 in 175,000 apheresis platelets, we have a report of a septic reaction and fatality of about 1 in 700,000, which is lower than the numbers that Dr. Dodd showed. So, it is reassuring that interventions are making a difference although more recent data has suggested that our current testing technology doesn't pick up very low

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levels of viable bacteria that do not necessarily modify very rapidly in blood. And the recent data suggests that the contamination level may be as high as 1 in 1,000, 1 in 2,000, apheresis platelets do have low levels of bacteria. So my question to you, Dr. Dodd, is, is it reasonable to expect platelet products to be sterile?

DR. DODD: Well, I think it's reasonable to expect it but unrealistic to think that currently available technology will do that.

DR. BRACEY: Dr. Kuehnert?

DR. KUEHNERT: Thank you for that talk, Dr. Dodd. I think, my question is, I'm just wondering -- because this is going to go to the Committee for discussion, at some point -- and, how would you say that risk should be prioritized? You skipped over that slide a little bit on the emergent infections program and what are the crucial elements but I think that's really important.

And, you talked about key infections, you know, for key infections the residual risk is such and such, agents of major concern, but should agents be a major concern when the risk is one in a million or shouldn't the risk be, agents of major concern be the ones where the risk is one in a thousand?

DR. DODD: Well, I think, Dr. Kuehnert, this is a perennial question. I'm certainly not equipped to answer it. I remember quite a few years ago the blood bankers were struggling with this question and they asked the Institute of Medicine to take this on and we had a wonderful meeting and lots of presentations, the sort you're going to hear today. And at the end of the meeting the Institute of Medicine looked at us and smiled at us and said, "You're smart guys. You're going to work this out." And, you know, it was a rather disappointing outcome of a great meeting and very high hopes but I do think that it's very important to have some sort of rational mechanism to achieve this.

And, I think the problem in my mind, to put it very simply, is that the two axes of public and political concern and public health risk don't necessarily meet. And, I think it's the task of a committee like this to try and find some way of working their way through this issue. Certainly those infections that are going to cause the most human damage in the long-term are those that really need to be locked at most carefully.

So, are you going to be concerned more about one in a thousand infections that really don't do very much or are very readily treatable versus one or two in a million that are going to cause a horrible, lingering death? The answer pretty much is sort of obvious, I think, but, it's a difficult one.

DR. BRACEY: Dr. Burdick?

DR. BURDICK: Thanks. This certainly was a very valuable presentation and I thank you. I would like to ask about the window. The window is typically thought of as the time from the point of acquisition, the moment of acquiring an infection to the time that a test becomes positive. Based on serological tests, that's where the concept came from.

But, with NAT testing both because the

window is clearly decreased considerably, in many cases probably, and also because the NAT testing is tied much more closely to the mechanism of infection, which is the number of organisms in the entity that's being transfused, is it reasonable to reconsider window period using NAT testing from the point of infectivity of the product to the time the test becomes positive rather than the time of acquisition in the donor to the time that the test becomes positive?

DR. DODD: Yes, I think it really is, and I sort of skipped through this rather lightly but in fact this is really the approach that Mike Busch has pioneered by suggesting that one should measure the window period from the point at which at least by extrapolation you would expect to find one particle, however defined, in about the usual amount of plasma that's included in a component, 20 "mils" or 40 "mils."

So, if you go back down to one, one genome equivalent per 20 or 40 "mils" of a potentially infectious compartment, that is, I think, doing exactly what you suggested. And I do think that's an appropriate way to go. I mean, we all know there's a genuine eclipse phase right after infection where it is very unlikely that the agent is going to circulated in the blood, at least in most cases.

DR. BRACEY: Dr. Sandler?

DR. SANDLER: As acknowledged, Roger, your talk was comprehensive and expert for the subject you were asked to address. But I think it's incomplete looking at safety without looking at the impact, the adverse impact that it's had on availability, our Committee of Safety and Availability. The risk to a patient coming in for a liver transplant today in my hospital has got nothing to do with what you talked about. It's got to do with, do I have enough blood to get them through the case tomorrow, and the scale, it has got nothing to do with the scale you presented. It's way over on the side of "I'm not sure." Even last week, I had no platelets for a period of time and had to cancel liver transplants at my hospital and a couple of times last year I waited seven hours for blood to come when someone was in the OR. That's a direct result of the nonspecificity of the efforts we're making to make blood safer in the world that you describe. The next time, Mr. Chairman, we address safety, I think it would be much more realistic to take the impact that safety has had on availability and look at the global picture. Thank you.

DR. BRACEY: Thank you. Ms. Finley?

MS. FINLEY: Thank you, Dr. Dodd, for really trying to scientifically give us some numbers on which to base on some of the important questions that we'll be looking at today and tomorrow. There is another issue here, however, that really lurks in the background and actually in the forefront of everything that we're doing and the issues and questions about safety and availability that we cannot put a number on and that's compliance.

Currently we are seeing what patient groups are perceiving as an increase in compliance issues. Particularly the letter from the FDA District Director, "Carol Heppin" (phonetic), to the transfusion industry, and also the fact that 50 percent of the nation's blood

supply is collected under a consent decree. If there were no human factors in this, if we didn't have testing errors, if we didn't have screening errors, if we didn't have these other errors it would be much easier to look at a number and say we can detect these infections and then rely on it. So, I wanted to get your input on the human factors and the compliance issues that very much have determined our reliance on testing regimens.

DR. DODD: That's probably another talk. I think that --

MS. FINLEY: Physical element of what we're discussing today.

DR. DODD: I would agree that it is an element and I think that just by measuring the frequency with which there's an absence of compliance, that doesn't necessarily translate directly and specifically into a determination of risk level. I take your point very much but I would say from the perspective of the testing arena, that's one of our priorities, to work with, to the largest extent

possible with issues that really take the human aspect out.

We like to have high-level automation. We like to have automation that collects all of the necessary quality data. I think that there are humans at every part of this chain. There are humans that come to give us blood. They don't always answer the question correctly, many cases for perfectly innocent reasons. There are people asking the questions. I don't think we can take the humans right out of it but I would submit that the difference between a compliance failure and a failure to provide a safe unit of blood is not an exact parallel. I think that we're spending a lot of time concerned about low-level compliance errors that really don't have a major impact. And I think it's fair to say that anytime that the FDA speaks about compliance issues, they freely acknowledge that

nevertheless that the blood supply is still safe. And
perhaps someone from the FDA would be willing to do
that today but we cannot quantitate it but it's there.

DR. BRACEY: Thank you. If there are no

additional questions or comments, we'll take a fifteen
minute break and reconvene at ten of. Thank you.

(There was a break in the proceedings.)

DR. BRACEY: We will resume the meeting.
Our next speaker has survived the travails of travel
and is here to present a very interesting topic. The
next speaker is Dr. Marc Roberts. Dr. Roberts is
Professor of Political Economy and Health Policy in the
Department of Health Policy and Management at the
Harvard School of Public Health. He's taught
economics, statistics, public health, ethics,
management, environmental policy, public health policy
at the Kennedy School of Government and at the Harvard
Law School and the School of Public Health. He
initiated the first course on the philosophical basis

of public health policy to be taught at a school of public health in the U.S. He's a coauthor and author of many publications and his research has focused on environmental policy, health sector reform and the ethical aspects of these decisions. Dr. Roberts? The topic will be ethical considerations of transfusion and

transplantation safety.

DR. ROBERTS: Thank you, Mr. Chairman and members of the Committee. I apologize for the vagaries of the Transportation Safety Administration at Logan Airport this morning, the combination of fog, a garbage truck and TSA and the enthusiasm of U.S. Air for getting the plane off before the announced departure time. But actually, from my point of view, it was a fortuitous delay because I got to hear most of the previous, extremely interesting talk and several of the issues it raised which, in fact, I want to address and I now feel perhaps I can address in a more informed way, having heard that presentation.

Let me say I am not an expert on the

technical matters. I was trained as an economist although for the last 40 years I have been trying to give it up. I'm sort of a recovering or lapsed economist. And, I do now a lot of work for the World Bank teaching about health sector reform and working with governments around the world and so I often find myself on international flights. And when I fly

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internationally I try to read something useful and constructive but on a 14-hour flight after about six hours I relax with a mystery novel. And when reading a mystery novel, I read the first couple chapters and then on a plane I always turn to the end because I think it would be really terrible to have the plane to go down and not know who did it. You know, you wouldn't want to be, as the plane's going down you're flipping through the book, trying to -- it's your last -- so, in that spirit although we are not at any risk of having the plane go down, let me in the spirit of "tell them what you're going tell them, tell it to them, tell them what you've told them," let me try to summarize what I want to say.

I think the term ethics is widely misused as a polemical marker for things that people want to advocate for. I'm going to try to unpack the idea a little bit and suggest what ethics might mean in the context of your work. And, I want to confess in advance that the ultimate conclusion I'm going to come to is as strong on process as it is on substance

although I do have several substantive mid-level principles to suggest that I have tried to formulate in a sufficiently provocative way to keep your attention.

So, what do we mean by ethical considerations? In general, ethics refers to ideas in the society about what's the right thing to do. And I can't be any more specific than that. And in a diverse society like the U.S., we discover there is no general agreement about what is the right thing to do. Does that mean there's no guidance available here? I think we can go a step further. I think there are a number of basic albeit conflicting goals that are widely believed in this society to be important for policy. And, I think that by reviewing these ideas we can at least clarify our thought processes both for ourselves and for other people about how we're thinking about the policymaking process.

Now, there are lots of doctors and nurses in the room, and in clinical medicine, in clinical bioethics there has been this emphasis on developing so-called mid-range principles for guiding interaction

between doctors and patients. These are not fundamental, philosophical ideas and they're actually not specific policy guidelines; they're somewhere in between. They're maxims like respect patient autonomy or try to advance the patient's interests, autonomy, beneficence and so on, these mid-range principles. Any of you who have taken a clinical bioethics course will recognize these.

Now, mid-range principles call out for

elaboration in two directions, first of all, where do they come from and how do we know that we should respect them and second, what are their implications? But mid-range principles are useful in a practical sense for people who actually want to make decisions because they represent a kind of synthesis or implication from the philosophical literature. In public health policymaking we do not have any agreement about mid-range principles, unlike the work that's been done over the last thirty years in clinical bioethics.

And, but undaunted by the lack of consensus in the literature, I'm going to attempt to offer some

mid-range principles for the consideration of the Committee this morning. I'm going to begin by, for better or worse, doing a little bit of moral philosophy, then mid-range principles and then talk about their implications. I promise to go light on the moral philosophy because moral philosophy is an excellent way at 11 o'clock in the morning to put everybody to sleep.

I, myself, find that when I do fly eight or twelve time zones and have trouble getting to sleep, a book of moral philosophy, particularly any of you who are interested, Immanuel Kant, will put you -- Immanuel Kant and a glass of wine and it doesn't matter about jet lag, it's much better than Melatone and you'll be asleep in 15 minutes. So, I'll try to avoid the heavy-duty moral philosophy but we have to start somewhere to get to mid-range principles.

So, I'm going to talk about what I see in the literature, five broad philosophical ideas. The first is that a good policy increases the aggregate well-being of a country's citizens. This is the kind

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of philosophical idea called consequentialism, judge a policy by its consequences. And the particular idea comes from John Stuart Mill and Jeremy Bentham, utilitarianism, the greatest good of the greatest number, as a way of thinking about policy. And anybody trained in economics who has done cost-benefit analysis or cost-effective analysis, that's really efforts to apply this kind of a principle.

Now, to make it operational we need to decide how to measure well-being and how to add up the gains and losses. And, if you really want to know about that, you have to come to Boston and sit in on my eight-week course on the moral philosophy of public health decision-making, but for our purposes, that notion, trying to maximize the benefit of what you guys do, seems to me one important place to begin.

The second place to begin has to do with notions of equity and fairness. Because, if we just maximize total well-being, the greatest good for the greatest number, we run the risk of sacrificing some people for others. "Oh, guess what, you happen to be

too expensive to save. Too bad." And, I think there is a lot of concern in this society about notions of fairness and notions of helping the worst off. For example, what differences in access to healthcare are acceptable based on differences in people's economic and social status? It's clear to me, working around world, that different countries have quite different answers to this question, very different answers about how redistributive they're prepared to be but, nonetheless, I think this fairness notion has an important role to play along with the notion of what's the total. We just don't have to look at the total. We also have to look at the distribution.

The third idea, that we don't only have to worry about outcomes, about where we wind up, about people's well-beings, we also have to worry about people's opportunity, about respecting an individual's capacity for choice. Choice is an important value in America, it's an important value in moral philosophy, and this is both individual choice and collective choice. And, collective choice means, has implications

for political process, as we'll see.

This notion about respecting individual's capacity for choice often gets bundled in political rhetoric in the notion off rights. I have a right to make my own decision. I have a right to refuse care. I have a right to this or a right to that. Rights are a very popular rhetorical move in American political discourse these days because it appears to be an uncompromisable claim. And I promise to avoid the deep weeds of Kantian moral philosophy. I think that the notion that rights are uncompromisable is itself not right but, now, rights are complicated because they can be in tension with other goals.

For example, if people have a right to make their own decisions, then they have a right to smoke and drink and act in various ways that can injure their health status or injure other people. But, if we take seriously collective and civic choice as well as individual choice, respect for individuals means citizens have to know, understand and be able to influence the decisions made by their government

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because most fundamentally the government is there as an instrument of citizens. And, we're not that far from "We hold these truths to be self-evident, that governments are instituted among men acquiring their just powers from the consent of the governed." And that's what this argument is all about, obviously important in the U.S.

Now, in addition to total benefit, the distribution of benefit and people's rights, a fourth idea has to do with respecting a community's views and traditions about social arrangements. Community traditions can obviously conflict with the other principles I've mentioned. There are famous stories in the history of public health about when D.H. Henderson, who went on to become dean at Hopkins, when he was a young operative working on small pox control in India, busting in, in the middle of the night, to the house of a local religious leader who had refused to allow all his followers to be immunized against small pox, with the Indian police, and literally tackling the guy and his wife and throwing them to the ground and forcibly immunizing them. That was producing benefit at the cost of not respecting an individual's tradition.

But our previous speaker raised this question in an important way when he talked about his two axes of calculated benefit and what traditions in the U.S. are like. I perceive that some of his slides drawing on the work of Cass Sunstein from University of Chicago Law School, who has pointed out that, for example, Americans will pay far more to decrease a death from cancer than they will pay to decrease a death from any other disease of equivalent pain and suffering. And, so, deciding who is the community, who speaks for the community can obviously be very controversial but this is a fourth idea.

A final idea has been in a way pushed by feminist scholars in recent years, and it's the idea that in addition to all this stuff about calculation and aggregate benefit and fairness and all this, we need to respond to and be concerned about the particular individuals affected by this issue, that we need to deal with individuals with compassion. This runs the risk of nonuniform decision-making but it may in the long run actually improve consequences. And I have been pushed to recognize this in part by looking at the patterns of cost-effectiveness or, I should say, the lack of cost-effectiveness in resource allocation in healthcare systems around the world.

Every system I've looked at -- and in the last ten years I've worked in literally 28 different countries -- in every system I've looked at the society spends, quote, too much on treating people who are acutely ill and facing death. The cost-benefit of acute care always indicates it's much less cost-effective than our favorite public health measures like immunization and prevention and primary care.

Now, there are two possible interpretations of this, right, either that everybody in the world is crazy and stupid, or that -- which is a possibility, it's the favorite conclusion of most academics -- and the alternative explanation is that people are onto something, that cost-effectiveness calculations are missing. And, part of what they're onto is people don't want to die and they don't want Grandma to die and they're willing to do a lot at a critical juncture to deal with that kind of contingency. And sensible policymaking, I would argue, at least has to understand the potential conflicts between individual compassion and calculation.

So, where does that leave us? Well, I've given us five philosophical ideas -- focus on consequences for the well-being of individuals, worry about equity, individual choice, community traditions and compassion. And, each of these is rooted in a long and complicated philosophical tradition which I'd be happy to discuss over coffee afterward or even better if I'm still around at the end of the day over a glass of wine. Moral philosophy is much better over a glass of wine, and, since we now know that wine extends life by diminishing cardiac risk, which has been about the only really good news in behavioral public health in the last 20 years. I would be happy to try to improve your life expectancy at the same time.

But, the question is, what mid-range

principles do these idea imply? How can we go from very broad ideas to principles that in turn might inform the decision-making of the Committee? So, here's five principles. The first is, when you consider another policy, you have to consider the costs as well as the benefits. And I'm arguing it's unethical to not consider costs. It's unethical because the costs come from somewhere. The costs represent scarce resources raised from citizens, and if we increase costs, that means we're decreasing people's opportunity, we're decreasing their well-being, we're decreasing our capacity to pursue other programs. So, focusing only on benefits and not on costs I argue is unethical.

Now, this is politically very difficult. It's very difficult because beneficiaries always focus on benefits and not costs. And, it's a well-known pattern in the U.S. that concentrated benefits and diffuse costs produce a pattern of political action that leads us to over-provide for the potential beneficiaries.

And this extends well beyond the health area. There's a classic example, for many years the USDA had a subsidy program for people who raised mohair goats. And the mohair goat subsidy program was put in place in 1917 to support the raising of mohair goats because mohair was then an ingredient in the winter trenchcoats that the Army officers used in the trenches in World War I, and so we were busy building up mohair production in order to have enough mohair make overcoats. And, of course, it didn't go away for 65 years, right? Because nobody gave a darn about the program except the mohair goat producers, who, you know, showed up at the Agriculture Committee every year and lobbied for it and it wasn't that much money. It was a penny for everybody else in America, right?

So, that's the classic paradigm of concentrated benefits and diffuse costs. But, and often the beneficiary groups argue it's unethical to worry about costs. And I'm saying if the basic principle is maximize the benefit for society, it's unethical not to worry about costs.

Second, accept imperfect or risky policies when justified by the benefits. This is not a cost-benefit calculation, it's a benefit-benefit calculation, and a comment about the effect of increased safety on availability of blood is a perfect example -- that's why I was so glad to be here for the discussion -- it's a perfect example of exactly this principle. You don't only focus on possible adverse consequences but also on possible gains.

Again, to focus on only one half of the problem is itself, I would argue, unethical. It's not being responsible. We have been through this with the FDA's change in policy about cancer drugs and HIV drugs and being willing to approve them faster and lowering the standards because they're looking more at the costs of not approving than the costs of approving. We've been struggling with this issue in lots of policymaking areas but it means we have to worry about the cost of false negatives as well as the cost of false positives.

And, by the way, while there's an advocacy group problem with regard to the first principle, there's a

bureaucratic politics problem with regard to this principle, because from the point of view of a decision-making agency, a false negative does not produce bad cases that you are then held responsible for.

So, it's much easier to say no in some cases than to say yes, and there's that big asymmetry. And this applies to both uncertainty in the world, where we don't know what the risk is, and also to our uncertainty about the world, where we have limited scientific understanding.

Ethical principle three, prefer information, influence, and incentives to coercion where doing so produces reasonable benefits at reasonable costs. This goes to the "rights and respect" idea. Coercive policies are most defensible when avoiding large harms to others but you have to remember the evidence is information alone seldom changes behavior. And, if you want to use regulation to limit options, it's best to eliminate options that nobody really wants.

I mean, for example, think about airline safety, right? We license pilots and we don't allow airlines to advertise "Fly for less, our pilots aren't very good but we get you there cheap." Right? Now, actually, we do have an airline like that in the world, Aeroflot actually operates that way, which is why the Department of State and the World Bank won't let any of us fly "Aeroflot." But, and this is a serious issue when you look at the whole question of unlicensed practitioners in poor countries who are in the role of traditional medicine in Hong Kong; you see this problem about restricting options.

Part of what's at stake is using the government to decrease the transaction costs to citizens, making it easy for citizens to make decisions by providing information or ruling out risky options so that we don't have to spend a lot of time trying to figure out what options are risky so that we can avoid them.

Ethical principle four, protect citizens against both health and economic risks. This has to do

with the equity argument, ensure access to prevention and care to some appropriate minimum level. Now, as the previous speaker said when he talked about reasonable risk, what's appropriate minimum level, it's an exactly similar problem but at least if you formulate it that way you can then have a discussion. The principle allows you to focus the conversation. It does imply that we should finance services as a whole based on ability to pay because not financing services based on ability to pay leads us to be unable to protect citizens against financial risk.

And, by the way, we know that when we make people pay for things, the first things that they don't do are the things that are most important from a public health point of view. The first things they do are stop immunizations, and stop prevention, and stop annual exams, back to they're always willing to pay for Grandma, which is least cost-effective and willing to give up routine cost-effective preventative care. But it means we also need to view compassionately the citizens' desires to avoid death for themselves and

loved ones.

And, finally, transparent, accountable processes that are based on explicit reasoning. This is also a matter of respect for people. Given that the substantive criteria conflict, that maximum benefit and equity might conflict or maximum benefit and respect for individual choice might conflict, there's a great premium in at least making the decisions in an open way where the reasons for the decision-making are made explicit and where the decision-making body holds itself accountable for increasing rather than decreasing its own accountability, for increasing the transparency.

Because, this kind of process, which the political science literature has called deliberation, has lots of value. It guards against partiality and pressure. You know, you can look someone in the eye and say, well, if we really make it clear that that's what we're doing, we will come in for a lot of criticism. This is the old Thomas Schelling notion in bargaining that limiting your own power to give in to

the other side is sometimes a useful tactic. Do you really want to make this public? I mean, this is the whole argument about public accountability around earmarks, is part of exactly this conversation.

But, there's another point, which goes again to something that the previous speaker said. I believe that part of the responsibility of a democratic government is to improve the capacity of citizens for their own self government, to help people understand what the issues are, and people are not going to understand the issues if no one ever tells them honestly about what the choices are.

The first book I ever did, now 30 years ago, 35 years ago on the decision-making in EPA, we looked at, among other things, the decision that EPA made on the ambient air standard for ozone. And when you actually looked it through, it turned out that the standard was set to protect serious asthmatics, living at high altitudes, engaging in vigorous outdoor exercise. Right? So asthmatic joggers in Denver, that's, that's who -- now, you could argue that that

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was the right standard, right, but at least if you said this is the standard, that's what we're doing, you at least facilitate a certain kind of public conversation about competing benefits and costs as well as benefits.

We know that even open processes disadvantage less sophisticated and less well-funded groups. You know, who can afford to have someone representing them here, who has the data, who has the information? Even open processes are not fully fair. We've studied thousands of processes and seen that result over and over again but open processes are clearly a lot better than non-open processes in this regard.

So, where does that lead me in terms of having some suggestions for all of you? I've done this as a set of negatives. First, adopting every possible increase in protection regardless of cost is not ethical. Now, that doesn't say exactly how you have to balance the costs and the benefits and it opens up the conversation and I'm going to say more about that in a minute but I want to put out that principle. Putting

lower-income individuals at significantly higher risk than higher-income individuals is not ethical.

Here's another benefit-benefit, rejecting disaster plans because they lead to higher risks than nondisaster plans would not be ethical. In a mass-casualty situation if we're not prepared to lower the standards in order to get the benefits of having enough blood availability in the mass-casualty situation, we're not abiding by the principle of appropriate balancing or allowing policy to be overly influenced by narrow advocacy groups and economic interests. These are the sorts of things that would not be ethical. And believe me, Mr. Chairman, I'm in no sense suggesting that the Committee has made any nonethical decisions. I'm just trying to be provocative.

Now, for example, if you think about adopting every policy, possibly increase in protection regardless of cost, the previous speaker talked about the one in a million standard. I want to suggest for the Committee's consideration some further thought

about that. What is the right unit for thinking about risk? Because, if the Committee is going to compare the risks it imposes on the population with other risks in the population, the risk per transfusion event is not the right denominator. Because, after all, environmental risks are, and the risks on the previous slide of, you know, eating a peanut butter sandwich a week or whatever, those are lifetime risks.

And, so, that would really be interesting to try to, it's not particularly difficult but to start recalculating risks on a lifetime basis. And, when you start looking at lifetime risks, again, the comment was made, very difficult to make people aware of the magnitude of very small lifetime risks. It's hard to conceptualize.

Here's my favorite example. What's the lifetime risk that an average American will be killed by an airplane falling out of the sky, killed on the ground? The answer is well above one in a million, well above one in a million. Because between 30 and 100 people are killed on the ground every year, that's

between one in three million and one in ten million per year, over a lifetime, well above one in a million that you will be killed by an airplane falling out of the sky.

So, that goes to the point about

transparency and accountability. You know, if we say how safe is safe enough, I'm reminded of the famous joke of Henny Youngman, the great Borsch Belt comedian, walking down the street, and Henny walks into his friend, Max, and Max says to him, "Henny, how's your wife?" And he says, "Relative to what?" And when I teach public health, I think I call this the "Henny Youngman Principle" and I urge this on the Committee.

So, to conclude, the basic philosophical idea as an the mid-level principles they suggest are unfortunately often in conflict. That means there's no simple algorithm to the ethical answer. Applying them to specific situations requires skill and judgment and it's skill and judgment that can only be developed through an explicit consideration of the problems themselves. It's like doing case studies in management

decision-making or doing grand rounds with a surgeon and learning how to do a physical diagnosis or arguing about Supreme Court opinions in law school. It's a skill that is developed through practice and criticism over time in specific situations.

We know that different countries can and will strike the balance in different ways. Different countries are more or less egalitarian. Different countries are more or less willing to pay for safety. Different countries are more or less sympathetic to the whales. For some reason the Norwegians and the Japanese don't take the whales very seriously. I take the whales quite seriously myself. But, so what other countries do can be suggestive, provocative, indicative but not necessarily dispositive in terms of how they proceed.

And, finally, being explicit about the principles and tradeoffs that serve as the basis for the decision foster democratic accountability and help us, help you -- and me, in my much smaller way, since I only get 80 students a year -- try to advance the

notion that explicit consideration of ethical principles and being explicit about the basis for decision-making will ultimately increase the capacity of citizens for self-government. Thank you very much, Mr. Chairman.

DR. BRACEY: Thank you. If I could, I would like to ask your perspective on one of the points that I heard is the importance of engaging the citizens in terms of making these decisions, and this Committee is composed in such way that we have representatives that are representatives of entities or groups that may need components but perhaps not the broad U.S. population. So, what are your thoughts about, as we make these decisions, the composition and the process that we currently have, have we engaged the U.S. citizenship adequately?

DR. ROBERTS: Well, first of all, that's a very deep question and without having more detailed knowledge about the composition of the Committee, beyond than what was said to me, I wouldn't presume to judge the Committee's current composition specifically.

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However, I very much endorse the general principle that you raise, and the general principle which I suggested earlier is reflected in the fact that the organized tend to have louder voices than the unorganized and yet the views of the unorganized matter a lot.

And, it's a very difficult problem to find ways to elicit and involve the unorganized. There's a big literature on environmental mediation and conciliation directed exactly at the issue that you raise. And, some people, for example, in local community dispute processes have advocated, you know, trying to pick citizens at random off the voter list and get a random selection of citizens into the process so that you have the voices of the unorganized represented. I'm not suggesting that as a mechanism for the Committee but certainly the consideration you raise is well-reflected in the literature.

The first book on this by Bruce and Susan Ackerman from Yale Law School, which was about the Delaware River hydrodevelopment process, and it was called the Uncertain Search for Environmental Quality, it's sort of the first classic in the field, and I was deeply influenced by it because I grew up in Bayonne, New Jersey, a tough industrial town in North Jersey, and my Boy Scout camp was in the area. They were going to flood with that dam. And they pointed out by going to the meetings and seeing who spoke and seeing who was able to participate, just how unequal the force of representation was in that process. So, I think you raise a very deep concern that I would commend to the Committee's attention.

DR. BRACEY: Thank you. Dr. Triulzi?

DR. TRIULZI: Thank you for a very provocative talk. Having been involved in some cost-benefit decision analyses in the past, when we talked about cost we often get the hospital perspective or healthcare institution perspective versus societal perspective for cost and I hear you advocating that we need to consider cost. Can you comment on whether it should be the societal, whether it should be the healthcare institution or does both have to be considered?

DR. ROBERTS: This is wonderful. The first two questions point directly to two of my obsessions so I thank the Committee. The first thing I want to warn you about is most healthcare cost, quote, cost data is somewhere between imaginary and terrible. The reason why is that much of what you see in the literature is not cost at all. It's actually based on charges, and charges have a very only approximate relationship to costs. Also even when it is costs, they're typically based on what are called the Medicare stepdown form; they're fully allocated averaged costs which have nothing to do often with the actual incremental costs of expanding the service.

So, even the narrow cost data need to be treated very cautiously. That's why, for example, if you see data that says it costs $250 to see someone in an emergency room and you think to yourself how could that be, that's because of the kinds of issues that are at stake.

I believe a comprehensive assessment of, let us say, impact is appropriate. The previous speaker talked about the problem of adding up in a way death and disability, and disability to many versus death to a few. And if you're going to do that in any kind of quantitative analysis, you need to rank health outcomes on some sort of comparable scale and decide how bad it is to not have an eye versus how bad it is to be dead.

And, there has been a lot of work on that. The WHO has developed this measurement called DALY, Disability Adjusted Life Years, as a way of combining certain kinds of costs but there are other kinds of costs that are also relevant that need to be thought about. So, I would urge a sophisticated and comprehensive measurement of impact.

From that point of view, having spent lots of my life playing that game both in the environmental area and in the public health area, I urge on the Committee the notion that these analytical techniques, because the available data are poor and our estimating ability is limited, these techniques are not very helpful in making close calls because the range of uncertainty around the estimates is so wide. They're much more helpful in thinking about, you know, is this decision really an order of magnitude out there, and really stupid? They're much better as screens for really bad decisions than they are as tie-breakers on really close decisions.

My former graduate student, Tammy Thames (phonetic) wrote a classic paper about the cost of 2,000 ways of saving a life and found that the least costly ways that we were doing through health and safety regulation and compared with the most costly ways, the most costly life-saving efforts were six orders of magnitude more expensive than the least costly life-saving estimates. Now, that's a big enough difference that it's probably real and it's worth using those numbers as a screen for six orders of magnitude.

DR. BRACEY: We'll have one more question unless there are other burning issues. Ms. Finley?

MS. FINLEY: Thank you. It was very provocative talk. Thank you very much. And while you're here I really wanted to get your opinion on a couple of 360-type issues that we will have to deal with later today. You raised the issue of Aeroflot. I thought that was a good segue into fear and perception of risk. I took them, flew them 30 hours last week.

DR. ROBERTS: You flew Aeroflot?

MS. FINLEY: I grade on the landing. The pilot got an "A", you know both times. It was great.

DR. ROBERTS: You're a "braver woman" than I am.

MS. FINLEY: It was one of the better flights I found. But getting to our issues, there are a couple of other issues that have come up in the history and the background of this. It would be great if it was so easy to say the cost of a life-year saved is "X" but behind all of this are other things. There's a perception by the Congress that the blood is a national resource, that we need this to be a strong healthcare system and that, you know, we expect this to be ever-ready.

There's an additional issue in the patient community that goes back to the fact that at the time

that decisions for critical issues for hepatitis and HIV, as well other transfusion-transmitted diseases were being determined, individuals were not at the table who had a strong interest in that. Patients weren't there. That's something the Institute of Medicine, the Department had agreed was a mistake and we're not going to do that in the future; however, there are some other issues here about risk and who assumed it.

The risk for a patient who receives a transfusion-related disease, the costs of bearing that are on that patient and, you know, whatever insurer they may have. There are blood shield laws in 48 of the 50 states that really limit the ability to take action against the blood banks. So, we still have no national compensation program for blood injuries the way we do for vaccine injuries.

And, so, I think there's a greater

imperative to test out, if we can, those risks as a result of that situation. The public has a strong interest in this in the sense that you and I as

taxpayers as well as everyone else at the table paid a half a billion dollars in the Ricky Ray compensation fund for the way that we handled the transmission of HIV. The hepatitis C issue is still out there and, you know, the patients are continuing to work on reparations for that. How do you think as a group we ought to address these issues knowing the level of complications? Do you have any suggestions for us at all.

DR. ROBERTS: Well, first let me say that whatever suggestion I have, it would not be for increasing the liability of the blood suppliers. I do think if you go back to the principle about protecting people against financial risk, then there's a pretty strong argument that if people are put really at risk in the situation we ought to worry about finding some way to protect them against that risk. Now, this is a complicated subject to raise, particularly in the middle of an election season because you get the difficult question about why should people be protected against that risk as opposed to all the other risks in

the healthcare system.

Someone, the previous speaker mentioned the estimate from the Institute of Medicine, "To Err is Human Report" that my colleague, Rushan Leubke (phonetic), authored about 100,000 deaths due to preventable medical error in the country every year.

So, it's a complicated question about should we protect people against these relatively few risks when people are not necessarily protected against other kind of risks. But from having put the question on the table, my own view is that the great may be the enemy of the good here and that protecting some people against some risks is better than, you know, than not protecting them against the risks even if there are other comparable risks that are left unprotected.

We do know if the Committee moves in that direction, I would urge you to pay attention to the experience of some other risk compensation efforts. And here I have in mind the Veterans Administration effort to compensate workers in the nuclear industry against radiation-related exposures for cancer. That

process has itself become very political. And, so, anybody who has been exposed to almost any radiation regardless of the extremely low probability that that radiation might have produced their cancer presses for compensation. I'm not sufficiently familiar with the details to decide whether the Committee is making the right or the wrong decisions but they have been, that committee has been under great pressure, once you open a compensation window, and we've seen the same thing obviously in the vaccine case.

So, this is an area where I think you need to proceed carefully and cautiously but in general my view is that more compensation for risk is better than less compensation for risk. And, by the way, insofar as we want the public to accept an imperfect system, compensation for risk may increase their acceptance of an imperfect system and decrease their pressure for perfection because if they're not compensated, then prevention is their only avenue.

Finally, your opening comments about public perception and the graph about the two axes that the

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previous speaker offered, I believe that one of the obligations of a committee like this is not only to react to public perception but to try to open a dialogue, a public dialogue about which of the current attitudes among the public is it appropriate for the Committee to respond to and which is it less appropriate for the Committee to respond to.

I mean, I think that's part of leadership on these issues, is not just say, oh, well, we think the public is nuts but the public cares so we're just going to follow along. This first book I ever did on EPA, the then-administrator of EPA at the time, the late Douglas Costle, went around the country telling people that if only they increased the appropriation for EPA, he would make them safe. And then when we got the SuperFund law and you got SuperFund sites that had cancer-causing chemicals leaking into the environment, and as we know the dose-response function for many chemical carcinogens is linear, so that there is no safe level, there is no threshold, you get very low risk from very low dose but the dose isn't zero.

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And having told people he would make them safe, he then had to go public meetings where people stood up and said, "Well, Mr. Costle, can you promise me that this site is now safe?" You have an obligation, I think, to help people calibrate their expectations in an appropriate way, in an interactive way where you think it's appropriate. Thank you very much.

DR. BRACEY: Thank you very much. We will now move on to our next speaker. He's well known to all of us, having been a former member of the Committee. It's Dr. Celso Bianco. Dr. Celso Bianco has been the Executive Vice President of America's Blood Centers, since 2000. Before joining America's Blood Centers, he was the Vice President for Medical Affairs at the New York Blood Center. Dr. Bianco has published many papers on membrane receptors of lymphocytes, macrophages, cellular immunology and broadly in transfusion medicine. Dr. Bianco will speak to us on the current landscape of blood diagnostics. Celso, welcome.

DR. BIANCO: Well, thank you for the opportunity to be here. I have a few little things in the beginning. First, I changed a little bit the title of the presentation to focus it on donor screening assay. The field of blood diagnostics is bigger than we can deal with. The second, I don't mean to be critical in my presentation. I mean to be challenging and I hope that your are going to be tolerant with me in what I am going to say. And the third and last thing before I start, I have been right only 50 percent of the time so I've been wrong 50 percent of the time. So, again I ask for some tolerance.

I think that I wanted to put this into context of safety and what, for instance, Dr. Ruta presented, that is the intent of the proposed rule and what Dr. Dodd really summarized in all the issues that we confront. And we talked, we learned from FDA, and actually, it is in the first few pages of that preamble to the proposed rule, the five layers of safety, are all these issues or layers in things that we do allow us to make sure that the blood that we transfuse is

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safe, donor suitability standards, donor deferral lists, testing blood for communicable agents, quarantining unsuitable blood and blood components, monitoring establishments by and reporting of fatalities or product deviations.

What we really have to ask ourselves as we are dealing with the issues of safety here and we are talking about several approaches to use, is what is the actual contribution of each one of these layers of safety to the safety of the final product? We tend to treat all of them equally and to say that each one is important. And actually, Ms. Finley asked about the issue of compliance and most of the failures in compliance are in other things that not tested. But really if we ask what is the contribution of each one of these layers, it is very small.

And I'll just raise some examples. Obviously this is not a treatise on that but we talk about medical history. There is an almost classical paper that Dr. Allan Williams, now with FDA, was the first author, that sent anonymous surveys to 34,000

donors as part of the "Regs One Program," and 1.9 percent of the donors reported deferral risks that would have lead them to be deferred at the time of donation. They wouldn't have donated. We have donor deferral risks and there is exactly in the last issue of Transfusion a very nice paper by Dr. Rich Cable and colleagues in an editorial just showing that donor deferral lists really makes almost no contribution. It doesn't make much of a contribution to safety. It's rational to do it. It's rational to have somebody that in the past had a positive test result or something that led us to disqualify them as a donor to prevent them from donating the last time but it's not a major safety measure simply to believe that this is going to prevent significantly errors associated with transfusion.

Quarantining unsuitable components, there was a very interesting analysis that was presented by FDA, by Sharon O'Callahan at the FDA Forum on Behavior-Based Donor Deferral Workshop, almost a year ago, that showed that over three years of the reports

to FDA, there were two inappropriate releases out of the maybe 20 million products that are distributed, out of the maybe 30,000, 40,000 positive products that were quarantined. So, essentially testing of blood for communicable disease agents is the major layer of safety. Most licensed screening tests have sensitivity and specificity that is above 99 percent. NAT reduced substantially the window period and the estimates of risk of HIV and HCV are based on testing and on window periods and the risk as Dr. Dodd very ably presented, is very, very small. So testing of blood for communicable disease is the major contributor and without donor screening assays, it's my belief, my strong belief, blood safety would be seriously compromised.

Well, how are donor screening assays treated or regulated in this country? I'm sorry. I out there, I said sorry for the superficiality to Epstein but I see Dr. Goodman, I see half of CBER is here and I should say I'm sorry to all of them. But the only thing I wanted to say is that donor screening

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assays, because of the seriousness of what the do, require a special process for licensure. They are required to be studied under extensive legal trials, rigorous review, each lot of the product goes under a lot release procedure and they are licensed by CBER. Diagnostic assays are reviewed by CDRH and are often approved under a simplified process, that is a 510(k).

There is a rationale for the difference. Donor screening assays qualify a unit for transfusion in the absence of clinical data. Diagnostic assays can be repeated if results don't agree with the patient's clinical picture. If I see a patient in an office and has the three grams of hemoglobin in the test result, I'll just call the lab and say repeat it, without charging the patient. And, we cannot do that with a unit of blood. We cannot withdraw the unit of blood from the veins of a recipient.

However, there are problems. We are strict, we feel comfortable, we feel that we are doing the best we can in terms of ensuring the safety of the blood supply but there are problems with the

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requirements for a biologic license. There are economics, regulatory burden, and ultimately it's all financed in economics here and there.

First, our industry is a mature industry. We collect about 15 million whole blood units in the country, and this has been flat for the past half a dozen years. We collect about 2 million apheresis platelets. They increased about 5 percent between 2001 and 2004. And we hope to have better data about that, in a new survey that DHHS is sponsoring through AABB. But there is little if any prospect for further growth. The manufacturers that make our assays, our tests, less than 1 percent -- and I'm being generous here, it's less than 0.1 percent -- of the revenue of Johnson & Johnson, Abbott, Chiron/Novartis or Roche comes from blood. The profit margins for blood screening are way below those of the pharmaceuticals that those same companies produce so their interest is limited.

The hospitals, and we had the little bit of a discussion with a question with Dr. Triulzi here, answered by "Dr. Marc," the hospitals are trying to run their business in best way they can under a somewhat limited resource environment in terms of healthcare. So, blood is also a small expense in general for the hospitals, less than 1 percent. About 5 to 15 percent of patients are transfused but blood shows up in their tables because it is the highest expense in the laboratory budget and that's where blood is placed.

The blood centers are all foundations. They are not-for-profit. There are no investors, being national like the American Red Cross or local like the ABC member centers. They work under low margins. They have low reserves and so they have limited ability to do themselves research and development. This graph actually is one that we have published in the ABC newsletter every year for many years, is how the price of a unit of blood, of red blood cells has changed over the years. This is adjusted for inflation.

It doesn't matter if you can't see the detail but each one of the things that we add, may be West Nile virus, NAT or bacterial detection or whatever will increase the price a little bit to what it is today, a little bit over an average of $200 for a red cell. I don't know how to compare that to the $5,000 for a dose of Factor VII-A. I don't know if Factor VII-A requires much more work or investment than what we invest in a unit of blood.

But, the values that society, actually manufacturers attribute to them are very, very different. And, because of that obviously the margins of blood centers, they have been excellent in the last three years. They are between 4 and a half and 5 percent, which is enough to reinvest but it's not enough to simply introduce totally new procedures that will increase the safety, automate more or computerize donor history, and all the things that we all want to do that would increase blood safety and would improve what we do.

I will try to go superficially about the current menu of assays available for donor screening just to make a point so I'm not going to get into details. There are two available platforms that are commonly used by all the blood centers in the country, with small variation. One is provided by Ortho, that is, from J&J. The other one is provided by Abbott. And, they use somewhat different methodologies. And in the past, most centers adopted a single platform. They were either an Ortho center or an Abbott center. More recently, because of a number of issues that we are going to see, there is a tendency to diversify in order to ensure assay availability.

But if we look at the assays that are available, when you look at this chart, the bars in yellow are the ones for assays that are currently in use and are adopted. There is one for each platform in the assay for hepatitis B surface antigen and there is one assay that was withdrawn and there is one assay that is moribund, that is, it should disappear in the next few months because the manufacturer has the newer assay and because FDA sets stricter standards of sensitivity for hepatitis B surface antigen.

For core antibodies to hepatitis B, also there are two assays that are remaining essentially in use. When we go to HIV 1-2, we have today a difficult prospect. There is one assay that Abbott has decided to remove from the market. The assay has been around since 1985. They have another assay that they are submitting for licensure but we don't know when and how, and this is in the hands essentially of the manufacturer.

I think that it is important that we mention that the initiative comes from the manufacturer; it does not come from FDA to license an assay. The manufacturer will approach FDA and say I'd like to have these tests reviewed and provide the clinical data. There are two assays in use for hepatitis C, but, and there is only one assay, moribund, that is available in the market today, that is the Abbott assay for HTLV-1, HTLV-2. For reasons that I hope Mr. Brian McDonough is going to discuss in his presentation, Ortho decided to leave the HTLV-1 area, and Abbott has developed an assay but again we do not know when this assay will be licensed and available for our use. Now, the nucleic acid testing is richer and we have two companies competing, GenProbe and Roche and most of the assays are available from both companies.

There are very few supplemental tests available on the market. There are still HIV Western Blots. There was a discussion a little bit this morning, they're old tests; despite being used as supplemental tests, they are less sensitive than the screening test and I think their value is somewhat questionable. And, but there aren't enough supplemental tests that would cover all the assays that we use for blood donor screening.

So, the conclusion that I make after examining this picture is that there are holes in the testing layer of safety. And, my question is, yes, we are very safe. Dr. Dodd told us that the risk for HCV, HIV is less than 1 in 2 million. But can we sustain that if we proceed with the lower interest of manufacturers into those assays, the difficulties of having new assays introduced in the economics of the system?

Among the holes are that there is a lack of

FDA-cleared additional more specific assays. There is simply no interest on the part of manufacturers to submit for approval of those assays. I got a call from a European company asking if we were interested, my members, in a confirmatory assay for HTLV-1 and HTLV-2 that is manufactured in Europe and I actually suggested to them to approach FDA and they told me that they were going to think about it because they estimated that the total market was $600,000 and they were considering if it was worth a trip to Washington for a couple of people in order to have this test examined and the cost that it would be.

And if we go to the side of organ and tissues, not all assays are cleared for organs and tissues. Even if they are used for that, they are essentially being used off-label. There are some requirements that are hard to understand like that tissues have to be tested by NAT with individual specimens, not pools like that is the routine that we use, when the same patient that is going to receive a bone marrow transplant is going to receive dozens of

blood products that were tested by minipool.

And there are other things more recently that have occurred that I find hard to understand. I know that if you read the package insert for West Nile virus, both tests from Roche and from Gen-Probe, Chiron and the test for T. cruzi, it specifically excludes testing of cord blood specimens. Well, first I don't think that anybody today would transfuse or would transplant a cord blood without having tested the cord blood or the serum removed from there or, for sure, even if there is the serum of the mother without passing for those things, because it would be unthinkable. But, I don't think that blood from a baby is that different from the blood from an adult, that you would need specific clinical trials to allow these tests to be used.

Dr. Leiby is going to talk later about

parasites and we don't have confirmatory tests. We don't have screening tests for malaria. We have one confirmatory test for T. cruzi that is based on analytic-specific reagents. And I personally have

concerns about this test because the antigens that are used in your additional screening test and in the confirmatory test are identical and I think that the ideal confirmatory test uses different technology, different attributes, different approaches.

For bacteria we have the other major issue. We don't have an assay for product release. The assays that are on the market, they have never been validated for product release. They have not been validated to say this unit was negative at the time it was tested for bacteria. The assays were developed for quality control and they are used off-label to define whether a unit of apheresis platelets is suitable for transfusion. But even if you look at every package insert of every one of those assays, none of them tell us what is quality control, how you do quality control to make sure. The only thing that is a suggestion from discussions and from ways that, for instance, the proposed rules are written is that quality control here would be testing 100 percent of the component by that test.

And, the available bacteria detection assays are not appropriate for random donor platelets. They are not pooled. And those are probably the most concerning of the products. They have received no focus from manufacturing or attention or ways to do it. There is a rapid-release test but it's a redundant test. It's a Virax (phonetic). It is test to be used a few hours before the transfusion but it has only been cleared for use of apheresis platelets that had already been tested by culture and found negative.

And, when I discussed these with the manufacturer, they said, oh, no, the requirements for licensing it, and in any other way are so big that we are not willing to go through it. They do not want to.

If the other tests that are available on the market didn't go through all these clinical trials, they don't want to go the same way and they're hoping that off-label use is going to provide them the return that they are looking for.

And, as were discussed here -- and Dr. Benjamin is one of the major authors -- many of the

recent studies show that the sensitivity of currently applied culture methods is limited because of low number of bacteria. Also, there the question why don't manufactures submit assays currently available in other countries for clearance in the U.S., and the reasons they give me is -- and again I hope Mr. McDonough is going to help us -- is that the licensure of screening tests costs an immense amount of money. They say at least $10 million.

Complex requirements for very limited markets, for instance, West Nile virus, if you were going to test in cord blood or to do a cadaveric specimen study when only a few thousand specimens will be tested every year, producing very limited returns, and for the clinical trials that, in which the informed consent process has been made stricter, and opt-out is one of the issues, in the donor, even if the test is being used at the center, the donor has to consent to the use of an unlicensed test, is very difficult to manage, and our recent experience is that more than 20 percent of the donors just say no, making it difficult

to carry out those trials. And, particularly when those tests are only applied to whole blood that is more restrictive; when they are apply to source plasma, then you double essentially the number of tests that are used.

Regulation is an issue that is raised by the manufacturers and there is concern. The current environment is risk-adverse because of the issues that we all know and we understand the pressure that FDA is under, that is, everybody tells them that they have to solve all the problems, the toothpaste, the pet food, or the Salmonella in peanut butter. And obviously this drives them to have low tolerance for risk leading to very strict measures.

And essentially in our field there is blood, there is the potential for one case, is equivalent to a rule being set for that. Last few weeks the cutoff for the Chagas assay was changed because there was one case, positive case, that was below the cutoff, one, that had been set for the assay. For West Nile virus we went to 120 days because one

individual had, in a few tests, a positive NAT after 184 days.

The manufacturers of tests, equipment and software, they are few and shrinking. There is limited competition, higher prices, less innovation. The stockholders that fund those companies are focused on short-term profits, so, they limit R&D testing and they only push for test development after the regulator is committed to mandate the test. Gone are the times when

Abbott, for instance, had a hepatitis research program in which they were looking for new antigens and new things. Today they are just waiting for FDA to say something at BPAC that will encourage them to invest in that test.

And there is low interest in venture capital because they have had difficulties in the past. The history of oxygen carriers and pathogen inactivation doesn't help. For the past 20 years, they have been, or 15 years, trying for that and not a single of those products has been brought to market, for a number of reasons, and, many even right reasons.

And for these and other reasons, devices have been introduced in the U.S. five to ten years after they were introduced in Europe and in other countries.

To close, I can say some thoughts. I don't know how to solve all those problems. I know we need to plug these holes. We need to create new layers of safety and we need to create alternative pathways for approval or licensure of assays with a very limited market, for instance, the confirmatory assays.

The centers themselves have to learn how to expand their activity beyond collecting red cells and do other things that may increase their value to the communities and organizations. We have to help stimulate competition among manufacturers to bring innovation and we have to make transfusion medicine financially more attractive for manufacturers of products for transfusion medicine. Otherwise, everybody is going to run away from our field; there is no reason for them to be there.

And we need to overcome the inhibitory effect that the recent U.S. history of regulatory

failures, the oxygen carriers and pathogen inactivation have had. We need some paradigm shifts. We need to educate the consumers. We need public discussion. We need to emphasize the benefits of transfusion. At least in my case, I'm alive because of blood transfusions and I believe that many people are and I believe that they have a tremendously important role in healthcare. We have to be able to communicate to the public also that when we are searching for new safety measures we are not saying that blood now is unsafe. We confuse messages and the public doesn't understand that. They don't understand when we talk about TRALI that the blood did not become unsafe today because of TRALI. We always had TRALI. It is that now we are addressing it. That's the victory. What they do is just to add this to the list of things that are bad about blood and to create more concern and more difficulty. And we have to challenge the precautions, the paralyzing precautions and other approaches that inhibit innovation. We need to encourage development of evidence-based policies. Essentially, I think that

we have to believe that "The future ain't what it used to be." Thank you very much.

DR. BRACEY: Thank you, Dr. Bianco, for that comprehensive review of the challenges that we face. We often speak of the fragility of the blood supply but perhaps we should consider the fragility of the blood system. In the interest of time, we will take a lunch break now and anyone that has questions or comments can entertain them with Dr. Bianco. We will reconvene at then 1:15, or 1 o'clock, because we have Dr. Wright coming, so, quick lunch. Thank you.

(There was a break in the proceedings.)

DR. BRACEY: If I could have your attention, please. We would like to resume the meeting. And, we resume the meeting with the introduction of a very special guest. I have the pleasure of introducing Dr. Don Wright. Dr. Wright is the appointed Principal Deputy Secretary for Health. He was appointed on December 2nd of 2007. In that capacity and as an Acting Assistant Secretary for Health, he is the primary advisor to the HHS Secretary

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on matters involving the nation's public health and science.

He's also responsible for oversight of the

U.S. Public Health Service and its commission report. Dr. Wright's responsibilities also include planning and execution of public health policy as it relates to disease prevention, health promotion, women's and minority health, the reduction of health disparities, the fight against HIV, AIDS, blood safety and pandemic influenza planning. So he's indeed a busy man.

Prior to becoming the Principal Deputy Assistant Secretary for Health, Dr. Wright served as the Director of the office of Occupational Medicine for OSHA. As a result of his leadership, OSHA now recognizes the impairment with drug and alcohol as an avoidable workplace injury. Dr. Wright has had training in Texas -- the Great State of Texas, which I'm also from -- and he has come here today to share some of his thoughts about his new responsibilities along with his continuing responsibilities in the HHS. Dr. Wright?

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DR. WRIGHT: Thank you very much. It truly is a pleasure to be with you today. As was mentioned, my name is Dr. Don Wright. I'm serving as the Acting Assistant Secretary for Health in the Department of Health and Human Services. You can probably tell by my accent I'm not a local here. I am from that Great State of Texas and I spent the majority of my career actually in the private sector, was invited to OSHA four and half years ago as Director of the Office Occupational Medicine and then was selected to be the Principal Deputy Assistant Secretary for Health. Just, I think this is my third or fourth week on the job so I truly am the new kid on the block but it is a pleasure to be here.

Let me tell you that, first of all, say, that I am inordinately appreciative of what you do, the fact that you bring your medical expertise, your subject matter expertise to this group and to the Department of Health and Human Services. And I say that on behalf of not only myself but of Secretary Leavitt. You know, we rely on the expertise that each of you have. And, there are so many examples of how your expertise has really affected what we do at the Department of Health and Human Services.

I know there are some newcomers to the Advisory Committee Board but I also know there are some long-serving ones. I certainly want to acknowledge the contributions of Dr. Sandler here, who is exiting the board, I understand, after six years of service. Dr. Sandler, we appreciate your work and your contributions that you made, the leadership that you showed to this group, and I know with you being just in Georgetown, you're only a phone call away if we need additional expertise.

Let me say that I've looked back. I am the new kid on the block and still have a great deal to learn as far as learning what this particular committee has done and will continue to do in the future. I know you've been very instrumental in looking at the strategic plan that my predecessor had you work on, Dr. Agwunobi. My understanding is that that's still in the vetting process and I hope to meet with you again at some of the future Advisory Committees and see how we can move forward as far as next steps of implementing the strategic plan.

I know that also much of the advice that has come out of this Committee has been very helpful for CMS as it relates to several different issues. Dr. Holmberg has made me very aware of his concern as well as the concern of the overall Committee as it relates to blood supply and tracking the blood supply in the midst of a natural disaster and how we don't have a good system to do that. Certainly that's a big challenge but one that we're open to looking at and trying to find plausible solutions for. It becomes increasingly difficult in the budgetary times we're in but it's one we certainly intend to look at and hopefully address.

I really didn't have a formal agenda to talk to you today. I wanted to introduce myself. I wanted to make it clear that on behalf of myself and the Secretary of HHS that I am exceedingly appreciative of what you do. We've counted on you in the past, we'll count on you in the future, and we could not do the job we do without your expertise. Dr. Holmberg thought that it might be appropriate that you may have a few questions for me. Now, I hope you'll go gentle. I'm only three weeks on the job. But, I'll be happy to entertain and questions and attempt to answer any questions that you may have.

DR. BRACEY: If I could take the Chairman's prerogative. One thing is that the Assistant Secretary has had a name that perhaps is not appropriate but the name has been "The Blood Tzar," representing the individual who would be the singular voice in this nation for safety of the blood supply and the availability of the blood supply. As structured this is an appointment that at times passes because of political issues but the blood safety and supply issues never go away. And so what is your perspective on having a continuous voice regarding availability and safety?

DR. WRIGHT: Very good question. I think one of the things I failed to mention to you is that I am actually a career employee, a career federal employee, not a political appointee. If you look over the history of OPHS, the Assistant Secretary for Health is a political position, politically nominated, and at various times within the history the individual directly under the Assistant Secretary, the Principal Deputy, the job that I currently have, has been held by a combination of career and political appointees depending on the administration and depending on the time.

I think if you look over the last eight years certainly there has been some transition from one leadership to another in the Assistant Secretary of Health realm and there was a feeling overall that there needed to be some consistency. And that's the reason that this particular administration decided to bring in a Principal Deputy Assistant Secretary that was a career individual, that would allow some consistency between administrations. So, for better or for worse I'm here to stay and hopefully can add a sense of consistency to the Office of Public Health and Science and be, provide a stabilizing force to that particular office.

DR. BRACEY: Well, thank you, we certainly welcome you. Other comments or questions from the Committee members? If not --

DR. WRIGHT: Well, in closing again let me just again express my appreciation for what you all do. I had an opportunity to look at your agenda and immediately felt how much of this can I listen to because so many of the discussions that you have are of vast interest. Unfortunately, the Deputy Secretary has indicated he needs me at a meeting at 2 o'clock today so I'm going to have to leave you. But again my sincere appreciation for all you do. I look forward to coming back and talking to this group and to share with you -- I know one of the things that you would be interested in is how are the recommendations, the suggestions that come out of this Committee actually put into practice and utilized within the Department of Health and Human Services. And I make a commitment to you to do that. So, thank you.

DR. BRACEY: Thank you. Okay. Then we move on to the presentations, continuation of the presentations for the afternoon. Oh, yes, I see our next presenter here. Our next presenter -- I just wanted to make sure -- is Dr. David Leiby. Dr. Leiby received a BS in biology from Lafayette College, and then an M.S., and a Ph.D. in zoology from Ohio State University. So I hope he's not feeling too down about Monday night's results. He has been a member of the National Research Council. He also has been very actively involved in the work of parasitology, being the Chief of Parasitology at the Biomedical Research and Development Center of American Red Cross, and has published extensively on risk related to parasites. Dr. Leiby will discuss unmet needs on the horizon, malaria, babesia, Dengue and others. Dr. Leiby?

DR. LEIBY: Thank you very much. I don't claim to be an Ohio State alumni even though I got my Ph.D. there. My wife is, though, and she was very disappointed.

DR. BRACEY: Okay.

DR. LEIBY: Thank you to Jerry and the Committee for inviting me to speak with you today. In the good faith of disclosures, as Roger alluded to earlier, Abbott Laboratories provides funding to the Holland (phonetic) Laboratory in the form of Center of Excellence, and some of that does indeed trickle down to my laboratory, and also I do some contract work for Navigant Biotechnologies.

I got the title from Jerry asking me to talk about unmet needs on the horizon, and he actually gave me, as you just read, a variety of agents to talk about, those being Plasmodium that cause malaria, babesia microti, which causes babesiosis, Dengue virus, Dengue fever and Dengue hemorrhagic fever -- see Mike, i can do viruses -- and they left open "other" and I didn't know what he really wanted me to do with that so I thought I would pick something on my own so I picked chikungunya virus. I think chikungunya is very topical. It's kind of fun to say, "chikungunya," and most of you probably know very little about it so if you get some facts and stuff and figures you can take

that home with you today, and if you're at a party this weekend you can impress your friends with your knowledge of chikungunya.

What is important, though, as we talk about unmet needs, each of these agents I'm going to talk about have an unmet need in a variety of different ways. And I'm going to try to provide you some data on how these are not met but how they could be met in the future or reasons why perhaps we struggle meeting them.

And I'll start first with Plasmodium, which is the agent of human malaria. As many of you know, there's four species of malaria, or the parasite Plasmodium, P. falciparum, P. vivax, P. malariae, and P. ovale that cause malaria in humans. Recently there has been a new one described, P. knowlesi, and which now has been talked about as a fifth species that causes human malaria. It's not a new form of Plasmodium, a new form of malaria. It has been known for quite some time but what is a new in a paper that just came out in Clinical Infectious Disease was the fact that what has long been described as Plasmodium

malariae cases in many cases may in fact may be this agent. And there's actually been some genetic work that shows the differences between these parasites. So, I think you will see more about this in the future.

This remains a concern for transfusion medicine because it's found inside red cells and liver cells, transmitted, as you know, by mosquitoes, primarily in the tropical and subtropical areas, and has both flu-like symptoms that include fevers and chills and certainly worldwide is a major concern, health issue, public health problem throughout the world and certainly causes a lot of disease and death.

Now, when we talk about this as a blood safety issue in the United States -- and I want to focus since 1998. And it's kind of nice, this is an older slide but now that we're in 2008, it's almost ten years. In that timeframe there have been less than five cases of transfusion-transmitted malaria, not very many. And so the question arises why have there been so few. This is something that we've had questions in place for deferred donors for many, many years. And it

raises the possibility that maybe the risk factor questions are actually doing a really great job and we're not getting as many cases, although there have been some studies even by the CDC's own admission that probably more cases get through because of the questions than they actually pick up.

One might suggest there might be demographic changes, that we're not seeing as many cases because the individuals who are now in the country who are coming into the country may not be from those areas where they are getting actively infected with malaria. Certainly in the seventies, even into the early eighties, a lot of Vietnam vets were certainly implicated in problems with malaria. We're just not seeing that anymore.

But in either case these empirical studies to support what really is causing this decrease in transfusion cases aren't really there, but what is becoming clear, though -- and I think Celso alluded to this -- is the importance that malaria is really becoming more of a blood availability issue as opposed

to a blood safety issue, which this Committee is very appropos to direct us to since it is on availability and safety. So I want to look at that issue.

This is data from the American Red Cross from the year 2000 through 2006 and this looks at the percent of donors lost due to various deferral criteria. These are the three criteria that are presently used throughout the United States where residents travel and having had malaria. And what you can see is a relatively few as far as percentage of donors lost were both residents and of course having had malaria but the number lost continually to travel has been increasing since the year 2000. And as Roger also mentioned on one of the slides, we're losing almost 100,000 donors per year because of this deferral. And I think -- and I'm going to provide some data, I think, that will support this -- Celso also mentioned by and large these type of questions, behavioral deferral questions really don't seem to work very well. And I think that's the crux of the issue with Plasmodium and malaria.

To look at this in a broader sense at the Red Cross for the last couple years we've been doing a study to try to understand how effective these questions really are, provide some of that empirical data that's missing. And we're using at this time a serologic test in the EIA, that's developed by NewMarket in the UK. It's the same test that the UK actually uses to test donors who are identified for risk for malaria.

One of the first things we wanted to do is we wanted to look at 3,000 nondeferred donors from the Greater Chesapeake and Potomac region -- that's in the Baltimore-Washington area -- to try to determine the background levels of EIA, how many false positives there were, and then we also wanted to look actually at deferred donors from Greater Chesapeake, those who were deferred for malaria risk and see if they're really infected or not.

We did some supplemental testing through PCR and RT-PCR. This is an attempt to identify donors who actually we can differentiate the various species

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they might have. And I would say up front that is very difficult and not very effective. By and large with many parasitic infections as true of malaria, babesia as we'll see, and in T. cruzi as well, the levels of the parasitemia are so low. It has nothing really to do with the sensitivity of the assays themselves as much to do with the biology of the organisms and the agents. They're much different than viruses.

And last we had a risk factor question in which we asked of our malaria-deferred donors and this has actually been a key component and actually has pointed out some inconsistencies and some of the problems and some of the inconsistencies with the current scheme.

This is the data we have to date and what we have is nondeferred donors on the left side. As you'll see we initially tested 3,229 donors. Using NewMarket tests, 21 were initially reactive and 11 were repeat reactive. So, you can tell that about ten of those were probably likely false positives, weren't really true positives at all.

What was interesting when we asked these donors and got donor demographics on these 11, we found with these nondeferred donors that we had tested at random that at least eight of those 11 either had had malaria or had lived in an area in which malaria is highly endemic. So, there are individuals in the donor pool who have had malaria and it raises questions are those donors at risk for transmitting the infection. And under the current process at which we screen donors through questions, those donors are not picked up.

When we looked at our deferred donors, thus far we've tested close to 1500 donors, 21 are initially reactive and 20 out of those 21 were repeat reactive. You can see it's a fairly different number, significantly different than the nondeferred donors. And what's interesting about those 20 repeat reactive donors, with the exception of one donor that was deferred for having had malaria, all the other ones were travel-related deferrals.

When we asked the question why were they deferred or what risk were they or what was their past

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risk, we found that each of these donors had a really complex kind of history. And we found among these 20 donors, they weren't just donors who have had travel, they hadn't just gone to Cancun for a vacation or to Luna, Mexico and then come back and were deferred. We found out that they really had rather complicated histories. In almost all cases they had also residence in a prior period. Many of them as you can see in this column had also had malaria at some times in their past life. And it's really these donors, these who are residents, and those who have had malaria are the ones at greatest risk for transmitting the infection in blood donors. In fact, in just about all the cases -- and I should have mentioned those five cases that we've had since 1998 all involved individuals who are residents who previously had malaria. It's not the travelers, that large percentage which I showed you on the graph, that hundred thousand that are deferred each year that are at greatest risk for transmitting malaria.

Of course the implications then of deferred

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and nondeferred donors, we have deferred and nondeferred donors with past history of malaria exposure and also, as I already mentioned, the nondeferred donors are not captured by the travel history.

Now, there's a lot of question about what these long-term antibody titers mean. In fact, some of these donors may be what is called semi-immune, and that's actually the relationship that's seen with many individuals who actually transmit infection. Those are the ones who are semi-immune. They have immunity, they show antibodies, but they still have the parasite present in their blood system. We don't know completely the relationship, what these long-term antibody titers mean to transfusion-transmission, and that's largely because, in the next bullet, their infection status remains unclear but what we do see is that travel-related infections have really a minimal, extremely small relationship to the actual risk of transmitting infection.

Now let me shift gears here. I want to go

through these four agents, since that's what I was asked to do, so I'm going jump from one to the other rather rapidly. Babesia is one you've heard about three or four times already today. And it's the agent of human babesiosis, one you may not have even heard of very well, certainly not in this area in Washington. You can see there it's also in the red cells. It sometime is mistaken for malaria because it has a very similar appearance.

In the United States the primary agent is babesia microti. There's another parasite, babesia divergens, in Europe, which causes human babesiosis. As I already said, it's in red cells and it's transmitted by Ixodes ticks, and those guys are down here in the bottom. These are the same ticks that transmit Lyme disease, also commonly called deer ticks. They also transmit several other agents, so, the ticks themselves can transmit three or four different kinds of pathogens, sometimes more than one of them. It causes flu and malaria-like symptoms but it can be extremely fatal in the elderly, the immunocompromised

and the asplenic.

I want to make it clear that as we talk about risks and different diseases -- and this came up, too, with Roger's talk -- sometimes you deal with an agent that occurs rather infrequently and has rather dire consequences versus one that happens more frequently but can be treated. In most cases babesia is treated with antibiotics rather successfully but there are many instances of elderly and the immunocompromised getting severe disease and dying. So those are the individuals who we're really concerned about.

I'll up Roger a little bit and I'll say there's greater than 70 transfusion cases worldwide. This is just since 1979. And, there has been one in Japan with a local variety of babesia microti found in Japan, endemic to Japan. There's one in Canada. We actually exported that case from here to Canada. Their donor came to the U.S., became infected in the United States, went back to Canada and transmitted the infection. But all the other cases have been in the

United States. It's actually ten per year, Roger, so you can up it each year by ten.

There has been one possible transfusion case recently described last year, B. microti in Europe. There is B. microti in Europe. It's just not well-studied or well-understood. And the recipients varied quite a bit from neonates to those 79 years of age. So, it's an infection that affects all individuals regardless of age.

Increasingly we're seeing more fatalities. I know within the Red Cross we've seen a couple fatalities this year and there have been several last year as well. There's also fatalities obviously outside the Red Cross system. So, this is becoming an agent that we need to be increasingly concerned about. It's transmitted by both red cells and platelets. We know its viability in blood products, both experimentally, in association with transfusion cases, is actually quite good. It's been shown to survive 21 days experimentally in blood, also 35 days in association with some transfusion cases. As also has been alluded to before, there are no licensed tests. There are no licensed tests; there are no interventions, other than the question have you ever had babesiosis and, of course, most people respond either no or I don't know what you're talking about.

So, quite frankly, there's nothing being done at this time to prevent this agent from being transmitted. And I think perhaps when Brian gives his talk next we'll also get into some of the issues about developing tests. In this case this is a very geographically limited agent, found primarily in northeastern United States, the upper midwest and perhaps the far west. How do you address -- and I know the FDA has struggled with this issue as well -- how do you address an agent that is geographically limited? This is perhaps one of the first times we have had to be confronted with this type of approach. Do you do regional testing? Do you do something else? And I'm going to come back to that thought a little bit later.

We have, though, seen in some of our studies at the Red Cross that this continues to be a problem. This is some of our data, and we've been looking at approximately 2,000 donors per year in the Connecticut blood region of the Red Cross since 1999. In this column you can see the annual percentage rate is about 1 percent of donors each year who are actually seropositive for B. microti. So, it's quite consistent with the level of infection.

We've also done some PCR in infected donors to see if they also have the parasite and this fluctuates from a high of 56, to some years it's been zero. But part of that has to do with when we get our donors and the ability to test them. We may test the donor after they've already cleared parasitemia and so we're only measuring antibodies whereas other years we're getting at the peak of the curve and we're seeing more parasitemic donors. But the bottom line is the donors are not only seropositive, they also have circulating parasites that lead to transmission cases.

And we have also been following donors on three-year cycles over the last several years, doing a natural history study, initially funded in part by the

CDC and we're looking at donors and testing them every 30 to 60 days looking at them by serology, blood smear, PCR, and also hamster inoculations, asking them risk-factor questions and trying to understand the relationship between serology and also parasitemia and also trying to see different infection patterns to see if those hold for these donors.

At this point we have somewhere between 75 and 100 donors who have either enrolled or completed this portion of the study. In about three-quarters of the donors we see this typical clearance pattern of this donor. First identified in July of 2000, they had a fairly high IFA titer, of 1 out of 52; a subsequent blood draw, for them, their titer had dropped but they were parasitemic by both PCR and hamster. With subsequent donations, the IFA titer decreased below baseline, and at the same time we no longer could detect parasitemia by PCR or hamster.

This is a very typical pattern of someone who acquires infection, develops parasitemia, the immune response kicks in and the parasite is cleared.

And for all practical purposes then this donor is clear of the infection, and probably is not at any risk at all for future blood donation. But presently as it is now anybody who has had a history of babesiosis is permanently deferred from future donation, which is odd because we don't do that for malaria.

We also see different types of patterns and this is one that I have actually termed -- and this is actually what the next slides two slides will be -- and these are the ones I'm more concerned about, and those are individuals who I think are chronic carriers. As you can see, go through the same kind of pattern early, high IFA titer, 1 in 512, they're parasitemic, in this case the donor was treated for babesiosis. Apparently we no longer see the infection or parasitemia but the donor maintains a very high antibody titer for years. We have probably 20 or 30 donors that we follow that for a period of as long as we follow them, for three years or longer, maintain a high antibody titer.

There was a relatively interesting case which we worked on with the NIH, with Harvey Alter's

group, of a donor who, at NIH, had a persistently long infection, a marathon runner and so forth, who actually had a chronic case of babesiosis, didn't know it and infected several individuals. So, this can go on for years and years and years without the knowledge of the individual.

Now, this is one subject we found particularly interesting. This was Subject 367, 79-year-old male, once again, similar pattern, high IFA titer, as high as 10 to 24 throughout most of the period -- that's three years -- very parasitemic early on by PCR, RT-PCR, hamster, and also blood smear. He was the only individual we have ever identified by blood smear. In order for him to be infected by blood smear he must have had a whopping infection.

What was interesting, after his treatment, when we went to test merely by standard PCR methods we saw that we only found him to be positive one more time by PCR but for all intents and purposes he appeared to be negative. When we developed a more sensitive and specific RT-PCR, we found that other times throughout

that same period he came up positive. So, here's this proof that we have these individuals who have these chronic infections, they have high antibody titers and they never cleared the infection. And these are the individuals who are probably ones transmitting a large portion of the infections.

When we looked at some of the transmission patterns in blood recipients in some of our studies, again through the same study period, this is really data revolving around lookback investigations, and gives you the number of donors tested and you can look at this all later in more detail. Again the IFA positives and the percentages were generally at around 1 percent; those tested by PCR had PCR-positive rates. What we saw, though, is in the early parts of our studies when we were identifying these donors for the first time an we implemented deferrals for donors who were either IFA-positive or PCR-positive, we started taking those donors out of the donor pool, in particular those chronic carriers who I just showed you. And as we pulled those our over the year we

noticed not only did our PCR-positive rate drop but the number of lookback positive cases dropped to zero, from 5 out of 17, 3 out of 13, so that we haven't found a positive lookback through this method since 2003. So, I don't have any empirical data that shows that this has direct implication but suggests to me that removing some of these chronic carriers from the donor pool is having a significant impact on blood safety.

Now, I want to switch gears for the third time, talk about something a little different and that is Dengue virus. Dengue virus is an arbovirus composed of single-stranded RNA. It's the etiologic agent of Dengue fever as well as Dengue hemorrhagic fever. There's approximately 50 to 100 million cases of Dengue fever per year in the world. That's a huge burden.

There's also several hundred thousand cases of Dengue hemorrhagic fever. It's transmitted by mosquitos, Aedes aegypti. There's a nice picture of the mosquito, the female mosquito taking a blood meal down below. There's four serotypes of Dengue, Dengue-1, 2, 3 and 4. You can in fact get all four Dengue specie subtypes.

Each time you get one, you have immunity to that same subtype but if you became infected with one, you still can get infected with two. Once you get infected with one and two, you can still get three and four. And as has been suggested before, there have been transfusion cases reported for Dengue virus.

The worldwide distribution of Dengue, as you can see, is throughout the southern part of Africa, through Asia, through South America, and increasingly up through Mexico and even into the United States. So, at least the yellow part are areas with infested Aedes aegypti mosquitoes. So, this is a concern that of cases that we haven't seen in the United States but presents a problem of something that is likely to occur and something that perhaps we need to address.

When we talk about Dengue fever and Dengue hemorrhagic fever, the characteristics, as you probably know, are fever, headache, myalgias, arthralgias and hemorrhagic manifestations. There's approximately a 5 percent case fatality rate and worldwide it's considered to be a resurgent disease. There's about

100 to 200 cases introduced into the U.S. each year. These are individuals who come to the country who have already had Dengue. And there's also now been localized transmission in the United States, which first reappeared in 1995.

So, we do have transmission in the United States from mosquitoes to humans. So, the great concern is that Dengue is going to sort of explode or actually move through the country, perhaps like West Nile but perhaps not, but the risk, of course, is there.

If one looks at the cases of Dengue

hemorrhagic fever in the Americas since 1970 -- and this slide comes from the CDC -- reports by thousands the cases in the seventies, eighties and nineties, as you can see, the rather dramatic increase of the current outbreak.

Now, there's a rather nice study that was done by the CDC and Red Cross together -- it was by Mohammed of the CDC and Sue Stramer at the Red Cross -- looking at the ability to detect Dengue nucleic acid in

blood donors in Puerto Rico, where there is plenty of Dengue to be found.

This study was done during September-December of 2005, involved all blood donations collected at that site. It was also collected immediately after the peak transmission season so it was really set up to try to identify those donors who might be infected of Dengue. And testing was done using a NAT test for Dengue RNA and it was a test by GenProbe and if they were positive, they were considered positive if they in fact were repeat reactive.

And then supplemental testing was done by PCR to determine the actual serotype. And what they found in this study was they tested over 16,000 donor samples, and out of that 12 were actually NAT-positive or .07, where that comes out to be 1 out of every 1300 donors were in fact positive. Three of the 12 actually lacked IgG, which suggests these are rather recent or acute infections. Four even had quantifiable virus, three were DENV-2, and one was DENV-3. And this

suggests that further on, actually three grew out mosquito cell cultures as shown here. So, at least with these four individuals they have active virus growing in them in the blood that was actually not only measurable by NAT testing but also through culture methods.

What was important then was that when you looked at some of the demographics of these donors they didn't cluster in any one area in Puerto Rico and there's also no relationships with donor demographics themselves. So, here's a threat that's in large parts of the Americas at this point. We know that there have been cases transmitted by blood and we can also demonstrate in blood donors the nucleic acid and the agent is actually there, which suggests this is a growing problem and one that we need to be concerned with in the future.

Now, as I promised my last one to be something completely different for you, which is chikungunya virus or "chik-v." It was first identified in Tanzania in 1953 so despite everything you hear

about this being some new emerging agent, like many other agents we deal with, it's been around for a long time. It just hasn't made its ways to the United States so we haven't had any concern about it yet.

It's a zoonosis, primarily transmitted in Africa between primates and humans, but in this case we're going to see a little different lifecycle set up.

As I said, it's the etiologic agent of chikungunya fever, which is actually a Makonde word, which is a Tanzanian dialect, or tribe, meaning "that which bends up" and that actually refers to the fact that part of the disease or part of the symptoms or the result of this disease is very severe arthritis so people are bent in kind of funny ways.

It's primarily found in developing countries, in Africa and Asia, transmitted by mosquitos, primarily by Aedes aegypti and to a lesser extent Aedes albopictus. And this will come back as an important point because of the Italian outbreak I'll discuss and also because of the growing populations of the Aedes albopictus, which is actually the Asian tiger

mosquito in the United States. It causes mild to severe disease, with high fever, rash, painful arthralgia. The incubation period is three to seven days, acute fever is days to weeks, and it actually confers lifelong immunity.

Now, between 1952 and 2006 when you talked about chikungunya, as I already alluded to, it primarily involved countries in Africa, those in India and in Pakistan, and other parts of Asia. This was the known distribution of chikungunya. All that changed with the outbreaks in 2005 and 2007. And as I said here, the awareness actually became heightened in 2005, and largely as again with many of these agents it's because for the first time it actually appeared in developed countries.

Many times when these agents are found in developing countries we tend to ignore them. They don't seem to have much public health impact to us so it's not something that a lot of the larger countries worry about. Now when it develops into one that's found in developed countries, we begin to worry.

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When it first appeared on the island, La Reunion, which is actually a French -- I don't want to say colony, whatever the appropriate word is -- department, thank you, French department -- and it actually turned out then that 40 percent of the population actually became infected with the chikungunya virus. And so the French government became actively involved and made a lot of effort to try to stem the tide of chikungunya.

More importantly and actually more perhaps sinister is the fact that chikungunya was described from Italy as well, as recently as last year. There was actually, I believe, an immigrant who came into Italy with chikungunya virus and that was transmitted locally by mosquitos, in this case the Asian tiger mosquito. It's also been more in the news because it has now become associated with more severe disease and mortality. There has now been described transmission from mother to child, respiratory failure and actually brain infections.

For a long time chikungunya was thought not

to be a very serious disease, was actually even described as a benign disease by some individuals. There was actually an interesting article in Science talking about it a couple weeks ago where it said that in two years' time they've learned more about chikungunya than they had in the past two decades. Here again it's something that's in the forefront in the developed world now as opposed to the developing world.

And what they've also found is that the recent outbreak may in large part be due to a point mutation in the agent itself. Single amino acid in the envelope protein has changed. This leads to a 100-fold higher virus concentration in the salivary glands in the mosquito so that which each bite they're transporting more of the viruses which makes infection more likely. As I said, the Asian tiger mosquito has been implicated and USAMRIID is actually, some individuals are looking at USAMRIID's vaccine. They have a very old vaccine, at USAMRIID, that shows some possibility that might be used in the future.

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The reason why I talk about the Asian tiger mosquito, if you look at the map of distribution of Aedes albopictus in the United States, the Asian tiger mosquito came first from Asia into Houston in some tires on a ship and then quickly spread from there. And this is the current distribution. It's kind of funny how they seem to stop at the Virginia, North Carolina border but apparently they got across somehow. And there's growing numbers of these Asian tiger mosquitos. So, the fact that the vector is here, much like in Italy, poses the problem that, much like West Nile virus, we may at some point see chikungunya virus in the United States.

So with my last slide, just to summarize this up and maybe pontificate a little bit about where I think we are and what needs are unmet -- and I know Celso called it holes but I'll do it a little differently. I'll say there are some chinks in the blood safety armor. In some cases, I think in the case of malaria, I think the approaches we use are misdirected approaches. Malaria -- and I've said this in the past, I think -- the long-standing approach was to use questions in order to defer donors. And this is an old policy that we continually amend by adding new questions, whatever is the latest outbreak. In the end it really affects blood availability and has not done much for blood safety.

Then there are those that are indeed unmet challenges like babesiosis, 70 some cases at this point, new cases every year, is in deaths, but at this time we're not really addressing the issue. Why we're not doing it is really a complex issue. As I said, I think Brian might get into this. It is interesting, manufacturers are developing a test that may not have a universal market. It may have a regional market. It maybe for one that doesn't appear to be as serious as like HIV but these are the questions that we actually need to address.

And also in chinks -- and this is also going to be a chink, I think -- is newly emergent agents. How can we predict what will be the new emergent agents? Can we predict? Where will they come from? So, I really think it's time to think "out of the box." And what it really means is the existing models are ineffective. And what I mean by that is the models that we've applied before have largely been for viral agents, largely for viral agents that are spread across the population, so, it was easy to just implement a new test, test everyone and we increased or ensured blood safety. At this point with regionalized agents, even if chikungunya arrived in the United States, you've already seen it may only be limited to the southeastern part of the United States. So, we may deal with geographical issues. We may deal with populations of individuals who are at greatest risk for transmitting infection.

So, we have to come up with -- I know the word's popular, paradigm but we have to come up with new paradigms in new approaches. And that's why I said at the end we have a need for novel approaches. This may include agent-specific interventions. We may have to talk about pathogen reduction. Of course, that's why we're all here. And another option is look at multiplexed proteomics, some way of putting tests together in groups as opposed to having individual tests for each agent, having a broader list of agents that can be screened by one assay.

And I should be negligent if I didn't acknowledge some of the individuals who worked with me on these studies, at the Holland Lab, Laura Tonnetti and Megan Nguyen; the Red Cross region, who does lot of work on babesia, Richard Cable, Stephanie Johnson, Russell Melmed, and Jonathan Trouern-Trend; and the staff over at Chesapeake & Potomac, who works on malaria, Joan Gibble, Tami Goff. Thank you.

DR. BRACEY: Thank you, Dr. Leiby. Questions or comments from the Committee members on this? Yes, Dr. Klein?

DR. KLEIN: David, thank you very much. You talked about regionalized approaches but I would point out, as you know only too well, that the case at NIH of transfusion-transmitted babesiosis was from a donor who acquired it in the New England region, and certainly the Canadian case as well. So not only do agents move by mosquito but they move when people move as well. Do we have any idea about the mobility of blood donors and what kind of a potential risk this might be?

DR. LEIBY: Harvey, you point out a very important point. I mean, that's why I said, there has to be thinking "out of the box" and these raise some very difficult issues not only with the blood donors but blood products move, too. Blood products that are collected in Connecticut may be shipped to a nonendemic area across the country and transmitted. I don't have the answer about how often blood donors move. I would think in general with the general population, being a very mobile population, that blood donors move quite frequently.

I mean, how many people in here can say they're actually natives of Washington, D.C.? Probably not very many. And, so, we as a population tend to move and go other places. And so when you're dealing with imported infections in some cases or ones that are from regionalized areas in the United States, in which they're endemic, addressing them is extremely difficult.

DR. BRACEY: Dr. Benjamin?

DR. BENJAMIN: Dr. Leiby, you mentioned the problem with regional infections but I guess we should also discuss infective agents, the risk with selective components. We've implemented Chagas disease testing based on essentially seven transmissions in the U.S., caused probably by platelet products. We have yet to show any evidence of transmission through lookback study by plasma or packed red cell products; yet, we are testing, we're doing universal testing for Chagas disease. I'm sure there will be other components where the selective components show increased infectivity and again there will be little incentive to develop assays for universal testing when the risk isn't with universal components.

DR. LEIBY: You're correct, Richard. I mean, I'll argue with you -- and we've already done this before -- we think T. cruzi is probably also transmitted by red cells, but you're exactly right, the

seven cases are likely implemented or a target or implicate platelets although there have been whole blood transmissions as well. I mean, you can make the same kind of argument with babesia or malaria, organisms that live in red cells, primarily a red cell problem, certainly with red cells and platelets.

I think your question and Harvey's question just show some the complexities with some of these agents, and that's what I was trying to point out that the old thinking, which is merely just to get at viral infections that spread across the broad expanse of the country with population, was very easy to test everyone universally. Now we're getting into questions, I'm not sure if it's because the agents are more difficult or because we have whittled away the easy ones and now we're addressing the ones that are more difficult, the questions become more difficult. And I think in the end the solutions probably become more difficult as well, trying to piece together what is the best strategy, most cost-effective strategy, and so forth, all the topics we discussed this morning.

DR. BRACEY: Yes, Dr. Ramsey?

DR. RAMSEY: Thanks. With regard to the restrictions on travel related to malaria has there been any consideration of eliminating the travel restriction on Latin American travelers because of the risks of malaria in those returnees is vastly lower than from Africa, for example?

DR. LEIBY: The FDA had a workshop -- and Jay can correct me -- that was I believe 2005 or '6?

DR. EPSTEIN : '06.

DR. LEIBY: It was just on malaria and it discussed many of these very issues. And that's a topic that comes up quite frequently because if you look at the CDC data as far as malaria cases in the United States, and let's use malaria cases in the U.S. as a marker suggestive of what's going on as far as transfusion-transmission. The malaria cases in the

U.S. are almost by and large all from Africa. They are not from as you say Latin America and certainly not from travelers that go to Latin America. By and large our deferrals are for individuals who go to Latin

America and exposures there, so if there is a way I would think to eliminate travel-related deferrals, that would go a long way to increasing availability with having very minimal impact on safety. Jay might argue otherwise but I think travel questions in general, if you could really focus I think on residency as well as those who had past malaria you could cover almost a hundred percent of those who are at risk for transmitting infection.

DR. BRACEY: Go ahead. Dr. Kuehnert?

DR. KUEHNERT: I just wanted to ask, why do you think the fatality reports due to babesia are going up? Because at least in Connecticut the prevalence is the same.

DR. LEIBY: That's a good question as well.

In part it might be the practice of where the blood is going, as the population is becoming more elderly so that more elderly individuals are getting transfusion. Many of these cases that we've seen are individuals who are in their eighties or seventies who are more at risk or susceptible for infection. Babesia is not in

essence to limited to New England. It is slowly -- its geographic range is increasing. It has been described in New Jersey and I would venture to guess it's probably in Connecticut as well. It's a quote I always use and I like it but it's from a guy at -- I think Andy Spielman was at Harvard, right? Yes, he was at Harvard. He's now passed away but he was a very well-known infectious disease guy who worked with ticks and he always described that, "Lyme disease moved on the wings of birds and babesia on the backs of mice." And it has to do deal with how they pass through the ticks and are able to transmit the infections. And actually the ticks that attach to birds can contain Lyme disease, so Lyme quickly moved across the country.

With Babesia, because it doesn't pass through that stage that's on the birds, it has to go on the backs of these small white-footed mice. But slowly but surely babesia is widening its range. I mean, it originally started in the islands off New England, moved into Connecticut and then throughout New England. So part of it, too, is probably recognition. There have many

cases where babesia was misdiagnosed as malaria. Now we actually have the opposite occur as well. And, so, I think physicians are looking for that possibility of babesiosis and I think public health and education are getting better at it, too. But, those are all things that really should be studied, just not me pontificating.

DR. BRACEY: We probably need to -- well, Dr. Epstein, you want to go ahead and comment and then we'll need to move on to the next speaker. Dr. Epstein?

DR. EPSTEIN: Yeah, well, I just wanted to make a general comment. I don't really want to debate the specifics of any of the issues such as malaria but just to point out that, you know, the FDA is aware of many of the current limitations of our system and it's why we have been hosting a series of workshops to try to get our arms around the current issues and our current understandings, which have, after all, changed over time.

I mean, many of the policies that we're now

debating were well-accepted as the best that we could do at the time that they were instituted and our understanding of things has evolved, as, you know, better epidemiological work has been done, donor follow-ups, lookbacks, et cetera, and that our basic perspective is that we're interested in new ideas and we have a mindset of being highly proactive about scientific opportunities, for example, the discussion that we had at the malaria workshop about how to use serological testing and that there is an initiative within the FDA, that's called Critical Path, where we seek to apply research effort to solve the underlying problems that would enable regulatory paradigms to advance.

So, you know, the bottom line here is that we do have an open mind to new concepts but we also, I think, mindful of the remarks by Professor Roberts, we're balancing a set of conflicting principles as we try to move forward with, you know, the best answers.

DR. BRACEY: In line with the comments of Dr. Roberts, we are obligated to look at the cost of

these interventions and our next speaker will address economic factors of test development and implementation. Our speaker is Brian McDonough, who is Vice President of Worldwide Marketing, Ortho Clinical Diagnostics. He has spent the majority of his professional career in blood center management in both independent and Red Cross centers and he has a wealth of experience and we look forward to your presentation.

DR. McDONOUGH: Thank you. My disclosure

is that the following comments do not necessarily reflect the opinion of my company, Ortho Clinical Diagnostics, but I do have their approval and support for the expression of these comments.

My presentation to you is broken up into really four parts. One, I want to lay a fundamental common understanding, I guess, of how blood centers and public companies are both similar and how they are different, and, number two, by way of example, with diagnostics, I want to give you a perspective of what we refer to as market attractiveness. And in the third section, I'll go beyond diagnostics to talk about a

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broader subset of companies that support the transfusion medicine industry and then finally some summary comments with some thoughts about how going forward our respective worlds might begin to change in some of our behaviors in the way we make decisions.

Anybody can go online certainly to these blood centers and to any company and learn what their focus and/or their mission is. And, this is an example of four different blood systems operating in the United States. The similarity is rather common. Most all of them want to provide quality products, they want to provide blood components and related services and they want to do so on a very cost-effective basis.

Similarly, if you look at public companies like my own, Ortho, we all have similar vision statements or mission statements. We want to provide high-value products and services that support customers' missions to save and improve lives and to help manage and perhaps reduce the overall cost of healthcare.

So, on the surface it would appear that we

are collectively embracing the concepts of blood safety, of quality products, and cost of treatment, and I think that is true. But, there are, I would submit to you, some underlying business drivers that set us apart and separate.

For example, most blood centers strive for what we would refer to as self-sufficient. They want to be able to provide 100 percent of all the products that are required by the hospitals or the communities that we serve. Public companies are driven by the need to consistently grow year after year after year. You might even refer to it as an insatiable driver. Blood centers tend to operate in a monopolistic way, and I refer to them in large part as a public utility, much like the water company or the electric company or others. But, public companies of necessity and by design and desire are competitive. Blood centers strive to be low-cost providers, again following this utility model, but companies want to, what we refer to as sell at fair value.

Blood centers by and large -- and there are

some notable exceptions in the world, and particularly in the United States -- have a limited focus and expense in R&D. Public companies, on the other hand, have a very significant focus and expense in R&D. And, finally, blood centers are accountable to either a national authority or a local board of directors and public companies are obviously accountable to shareholders.

So, my summary of these differences is in these following statements: I think blood centers exist to meet the needs of community hospitals and thereby remain financially viable; again, the public utility model. Public companies exist to meet the financial needs of shareholders and strive to remain "mission viable."

Now, let me segue into the second section, which has to do with market attractiveness. This is a slide provided by Mike Busch. We've seen several examples of this of how over a period of time, certainly from 1984 to the present, the overall risk of the blood supply of infection due to transfusion has

been effectively reduced.

We also saw this slide from Celso earlier, and I've added some circles down at the bottom just to highlight those years in which a new assay was introduced to the market, that is to say, in those circled years blood centers began to test for an agent that they didn't test for before. In the intervening years on Celso's you will see that there are HCVO-2 tests and so forth. Those were improvements on the existing assay and the market didn't really grow as a consequence of that.

So, you'll see in blue these are essentially the serology assays. I've highlighted one in green, which is a serology assay which was introduced ex-U.S, but all the others were in the U.S., and the pink are two periods of time when we had NAT introduction. In terms of market attractiveness, both the P-24 antigen and the HCV antigen were essentially dropped from the menu of offered products as a consequence of NAT.

So, when you consider that and you look at

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the entire timeline, at least from the point of view of the serology market, from the period post-1990 through

2007, you wouldn't say that this represents a very attractive business opportunity. Certainly from the point of view of NAT, its introduction in late '99 and 2000 and augmented with West Nile virus in '03 has been a strong addition and, in fact, I think this graph or chart represents well, this would represent the blood community's perspective of the diagnostics market. Of the 80 some million donations that are tested worldwide, the total cost for that from providers is about 1.4 billion. It's worth noting or commenting that the NAT market, which now represents slightly more than 50 percent, is only about seven years old so from year 2000 to the current time, $700 million of new expense has been met by the blood industry.

This is how we see the in vitro diagnostic market, and you can see on the legend at the side that there are a number of different components to this, clinical chemistry, endocrinology, infectious disease is separate from donor screening, oncology, et cetera.

It's about $34 billion. But to highlight the relative perspective of the donor screening part of the total worldwide IVD market, it represents about 3 percent. Interestingly, this has been a common percentage for the last two decades.

Now, when companies like ours -- and incidentally, let me say that this data does not represent exclusive Ortho data. It is publicly available data if you know where to dig for it. So, this is a composite of data. IVD companies look today, at least in '07, and see a 34 billion dollar market. And you can see the relative size of NAT and serology for donor screening. By 2013 it appears to us that this market may grow to as much as 60 billion with a very significant increase in what we refer to as new biomarkers. I'll make a few comments about that in a moment. But, in general we see a significant increase in just the rest of the nondonor-related market, growing from 32 billion to 42 billion over this period of time.

Now, let's take a slightly different

perspective of this and let's assume that in 2013 this total diagnostic market looks like a 60 billion dollar market. And the issue is, what does this look like to two different companies, General Electric and Siemens? From their point of view, the entire market grows not just from 60 billion but to 120 billion when you add their current business and the future growth of their business in imaging.

And on top of that, when you add their current and future growth business in the area of information technology, from their point of view the entire diagnostics/imaging/information technology market looks like $185 billion. So, the fundamental question is, where do we think that these companies will look and invest for their future growth opportunities?

Let me take this slightly different point of view. This graph represents a fairly typical portfolio management graph used by many companies and it attempts to chart the reward versus risk or the relative probability of success of introducing a new product. And in this example I will use something called X-test, where a company has done an investment-risk analysis and the summary statements are that the health risk is well-documented and understood, at least from the point of view of the company, that a standard of care for implementing this new assay would appear to pertain, that there has been a regulatory or national, in some cases, funding authority assurance of action, and this particular company believes that they can be first to market, which is a fairly significant advantage.

What can happen -- and we take risks for these kinds of outcomes -- is that after the test has been launched, the standard of care has not been persuasive, at least not on the timeline that was originally projected. Despite the evidence of health risk, the market looks for ways to minimize adoption, something I think Brian will talk about later, in cost utility analysis, and in some cases the regulatory and/or funding action can be delayed.

Now, again this is a natural consequence of any company that's investing in the future of its business and we take these risks. What is different today or what I want to convey to you is that today there's a significantly higher level of competition for these investment dollars than there has been in the past and that from the point of view of diagnostics companies the relative risk of tests for the donor screening market carry a higher risk profile of adoption than they did in obviously the 1980's.

So, going forward companies have to look at their investment in a test, in this case, for "infectious disease Y," against other competing interests in four major fields of future interest -- cardiovascular, metabolic and oncology and hematology diseases. These are the four big areas, particularly cardiovascular, metabolic and oncology, where that wedge of the pie on one of the graphs I showed earlier of a 17 billion dollar growth over the next five to six years is expected to come from those particular areas.

So, in terms of market attractiveness, on the one hand we have donor screening, which Celso earlier identified as being low growth. There has been over a period of time discussions about the possible elimination of HBsAG in favor of individual NAT testing, the possible elimination of NHBC or core testing and perhaps even syphilis, and today we begin to hear and face more realistically the probability of selective screening strategies, whether it's over a period of time or whether or not it's for specific components.

Contrast that to what the market looks like for these new biomarkers. And I think Henry, Hank Nordhoff, who is the CEO of GenProbe, said this best on a TV show. He said all the new biomarkers and the driver behind the new biomarkers, the outcome is that earlier detection means earlier intervention and that produces better clinical outcomes for patients.

This is what we consider to be a high-growth area. There are a number of new markers targeted for early disease diagnosis and intervention. These markers do help predict disease progression and they help identify patients in advance of overt disease

manifestation. So, in terms of market attractiveness, this competition for dollars that have been heretofore invested in infectious disease testing for donor screening are facing some other very pressing medical opportunities in the world of general healthcare.

So, in an overall way I suggest to you that IVD companies are facing a shift, I think, commensurate with much of where healthcare is going, and that is away from a focus on pure laboratory efficiency and hospitals and blood center-focused in terms of our market and more towards disease-based interventions for currently unmet medical needs, focusing on clinical outcomes driven by health economics and a more patient and physician-focused orientation. So, consequently if you see diagnostic companies behaving differently, it is by design that we are doing so.

Now, let me segue to beyond diagnostics in this example. This is a list of companies that I have put together from a simple review of companies that have undergone some form of corporate structure or change in the last three years. Here are a couple of

reasons why companies go through corporate change. On the buy side a company will attempt to buy another company because they want to increase market share and that let's them in some cases leverage existing overhead costs and drive down their cost per units. They may buy a company because they want access to intellectual property. They may buy a company because there's a strategic focus shift and they want to be more broad-based than they have in the past and/or they want more what we refer to as channel-reach access, buy another company that can reach more customers than our current channel, which represents a growth opportunity for us, and also there are a number of companies that are bought simply because a group of investors believes that they can take this company, manage it more effectively, and then turn it around and spin it off for more profitability.

On the other hand, reasons to sell or merge, well, one, some companies sell a company or a division of a company to divest what are called "dogs," that is, nonrevenue or nonprofit producing segments of

their business. You may sell also for strategic focus. You are too broad-based and you want to narrow your focus and go for deeper penetration. You may sell to generate cash or sell a portion of your company to generate cash for debt or investment and again channel-reach and access for those reasons.

So, let's go back to this, and let me give you two examples. One that I find very interesting is the group in the blue box. Once upon a time, up to perhaps two to three years ago, I have at least known Haemonetics as a bag and plastic bowl manufacturer, pure-play company in the donor screening marketplace. But over the last three years they've now acquired three different software companies, IBM, Infonale and 5-D, and one other small company with a medical device to broaden out their focus of existence in serving in the market.

Another one is Siemens. Probably unknown to most everybody here but Siemens is now probably the largest diagnostic company in the world. They certainly are the number one market shareholder of

immunodiagnostics in the world and they have done so through the acquisition of certainly these three companies. Of interest to this audience is that only one of these companies that Siemens has acquired has any assays in the donor screening market and they represent less than 1 percent market share.

So, it's not likely, in my judgment, anyway, that Siemens is going to continue to invest a significant amount of money in infectious disease targeted for the donor screening market. That's not to say they're going to exit it entirely but this 70-plus billion dollar company, which is much broader than just diagnostics, I think has more broad-based interests. And, to a lesser or greater degree -- and you can read for yourselves every week that there are a number of different companies that undergo these kinds of changes.

So, summary messages. Number one, I've given this presentation or a version of it several times and invariably people say, so, Ortho is getting out of the donor screening business. This statement my

company does agree with -- Ortho is not exiting the donor screening business. We did drop an assay from our menu or will be dropping an assay from our menu of products and following an alternate business model but we are not exiting the donor screening business.

But, more broadly, I do want to say that suppliers do remain interested in the transfusion medicine market. What we have to understand is that there is now greater competition for the R&D dollars and that the profile of the transfusion medicine market creates higher risk relative to return compared to many of these other opportunities, again, low to no growth and, number two, a fairly significant amount today of ambiguity around what technology needs does the industry need and/or want to adopt.

So, what can you do? From our point of view, if and when the need for a technology intervention occurs, it's important to generate consensus on requirements and include and communicate with suppliers. And a good example of that is how West Nile and bacteria screening have been managed in the

U.S. Bad examples of that are CJD and pathogen reduction. And it actually occurred to me in the last day or so since I have said this that actually these may not be bad examples, they may be good examples of nonconsensus.

Number two, it's going to be important to define and communicate expectations for implementation. If it's the expectation of the market that a particular diagnostic will be used in all of the donors or subset of the donors or subset of the products, that's important information for a diagnostic company to have to make the decision about whether or not they can meet there and invest in such a product.

And, finally, in contrast to the history, I think, of the transfusion donor screening business in the United States, whether official or not, heretofore it's in large part been the practice that when a test is developed, we'll implement it broadly when both manufacturers have the test. That creates risk for diagnostic companies.

So, I would suggest that if a need is

identified, if it's been clearly communicated and understood that there is a specific amount of adoption that can be expected by the market, then the market should be prepared to act with first supplier approval because there are certain advantages that accrue to that and that helps make the business case obviously for a company that wants to invest and stay invested in this market.

So, what should you expect? On one hand I think you might expect over time some increased supplier consolidation serving the transfusion medicine market. You might also expect some suppliers to target R&D dollars towards other growth opportunities and the consequence of that is likely going to be less or fewer new technologies devoted to the transfusion medicine market. And you might also expect some higher prices over time.

Opportunities, there are a significant number of startup companies that find the transfusion and blood bank market attractive, companies promoting RFID, point-of-care tests, micro-array. Defined and

well-characterized opportunities that represent from a company's point of view low risk are also great opportunities, and here again the example is West Nile. Market consolidation can bring stabilization. A fewer number of competitors in a nongrowth market is better from the company's point of view and I think actually better from the blood center's point of view.

And, finally, the small customer base of donor centers throughout the world is really very attractive. In most of the diagnostics area we have, our customers number in the thousands. In the donor screening arena, in those 87 million donations, there are less than 1,000 customers and about 200 customers worldwide represent about 70 percent of the purchasing power. So, it's a relatively small market and customer base to be able to manage; and therefore, as I say again, it is very attractive, particularly for companies who have new technologies to bring, again, RFID applications, point-of-care tests, et cetera.

So, that was my last slide and I simply wanted to say that these represent again the

perspective of an individual who has worked on both sides of the aisle and these do not necessarily represent the perspective of my colleague companies but it is a synthesis of what I have been able to extract and review from commonly available documents and records from the industry and is just presented for your information. Thank you.

DR. BRACEY: Thank you. That was a sobering presentation. Dr. Sandler has a question.

DR. SANDLER: That was very informative. Thank you very much, Brian. In the world that I travel in, which is a very different one, and perhaps less enlightened than your own, I get this message all the time -- "You doctors are spending too much of our healthcare dollar on sickness and treating people who are in the last years of their life and we're going to take the healthcare dollar that's available in the United States, we're going to put it in preventative medicine." We're going to put it into public health."

The diagnostic tests that we do prevent disease and lower a lot of costs. If you prevent

someone from getting any of the diseases that are represented by blood diagnostic tests, you prevent transfusion-transmitted diseases, et cetera. How do you factor that movement, which is quite broad in our society, let's stop paying for terminal disease and let's start putting our money into preventive medicine; how does that fit into the model that you presented?

DR. McDONOUGH: Well, embedded in my comments was the focus on diagnostics companies today for new unmet medical needs. That's exactly where our companies want to go. The other side of the coin that I didn't articulate specifically -- but I guess can in form of opinion now -- is that infectious disease testing, infectious diseases tests are essentially a commodity today with the exception of new ones that come on the market and as patents expire and/or startup companies come into place, they bring and introduce these tests and that's how your costs can go down.

But the major drivers of shifts in the market, the Roches of the world, the Abbotts of the world, the Orthos of the world, the Siemens of the

world, the GEs of the world, they're looking at those new areas of unmet medical needs because that's where growth opportunities for them are and that's where there is the best opportunity to actually get ahead of the treatment curve, do intervention and overall reduce the total cost of healthcare.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: Thank you very much, Brian. I agree this is highly illuminating, and I have had the pleasure of hearing you twice. I'm going to ask you a question you've been asked before but I think it's important to elaborate a little bit, which is, to what extent does the picture look different to a small company?

Because, what you've described is how a large company looks at an array of opportunities and how they compete with what opportunities may or may not exist in the flat market of donor screening. But one would think that despite the flat market in donor screening that there are many niche roles that a small company might wish to capitalize on. So, why doesn't

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it work; why aren't there small startups for niche markets?

DR. McDONOUGH: There are a significant number of small startups and I will use an example in what we refer to as micro-array testing, to make my point, at least. There are a number of companies who probably have visited you and/or you have been at seminars, talking about their ability to do multiple assays on a single computer chip, fascinating technology, and I think one that will have significant, widespread application in the future world of diagnostics.

I do not think that that has any real potential application in our professional lifetime in the donor screening environment. And the following reason, the reason for that is that, number one, the art of finding an assay with exquisite sensitivity and specificity is not easy to do in a micro-allaquat of a blood sample, number one.

Number two, there is a very complex array of licenses and patents that these startup companies

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have to go through and get clearance for to be able to put a particular assay on their technology. Number three, the cost in the United States for bringing -- all the other problems resolved -- the cost for bringing a complete donor screening system to market, new system, six assays, including Chagas, approximates $100 million and there aren't very many companies who have that kind of capital to invest in a market that isn't growing.

So, most of these small startup companies have a good idea but in order for them to be successful they have to find a parent who can marshal it through the regulatory process and, number two, who have reaches into the markets all around the world to be able to produce that kind of return. And you can count the numbers of companies, certainly in the case of donor screening, certainly in the case of donor screening in the United States on one hand.

So, again, I think there are some great opportunities. A number of companies have jumped into the foray for bacteria screening because they saw a well-defined, well-articulated opportunity for bacterial screening of platelets. And, of course, they're going to try to leverage that and say we ought to bacterial screen all the red cells. That would be their growth opportunity. But I dare say, now that you have two and a half companies approved in the United States for bacterial screening, you won't see another two or three anytime soon because their approach to the market would be a one-time gain and no growth on top of that.

DR. BRACEY: Last question for Dr. Kuehnert.

DR. KUEHNERT: Yeah, that was a very helpful presentation. I just wondered if -- this is really to the previous two questions -- whether companies look at the ripple effect of screening donors as far as further tests that are needed to confirm disease and other diagnostics related to treatment because with sort of that effect created, Chagas might be an example where there's not a lot of recognition of Chagas disease in the U.S., donor screening starts and then all of a sudden there's recognition and desire for further testing.

DR. McDONOUGH: Chagas would be an example. And this again is not company reflection -- I need to be very clear about that -- but we use Chagas as an example. Most companies want to bring a test to the market as soon as they can. And, to the extent that you can target 95, 98, 99 percent of the need in your first generation assay, you move forward to do that; to get subsequent claims for 5-10-K or cadaveric and/or confirmatory assays generally can fall on a second generation.

Second-generation activities are typically a consequence of how well first generation behaved or performed in the market. If they don't perform as well as expected, the second generation will lag in some timeframe. So, you know, there is a connection there but my experience is that a company starts out with a complete plan for a thorough test for all the markets, diagnostics, cadaveric, I guess now stem cells, and confirmatory, but, their timeline for delivering among subsequent generations doesn't always come to meet the plan.

DR. BRACEY: Thank you. We'll then move onto the next speaker, who is known to many of us, particularly our Committee members, Dr. Mark Brecher. Dr. Mark Brecher earned a bachelor's degree in chemistry and his M.D. from the University of Chicago. He is trained at the Mayo Clinic in transfusion medicine and has a distinguished career in transfusion medicine. He's currently serving as the Vice Chair and Professor of Pathology at the University of North Carolina and he will speak to us on bacterial contamination of platelets. Welcome back.

DR. BRECHER: Thanks, Art. It's good to be back. I was asked by Jerry to cover a wide range of topics including the historical perspective, what's currently going on and possibly the future with specific emphasis about pathogen reduction. Since there is so much in the program on pathogen reduction coming up, I'm going to just gloss over that section but try to give the Committee somewhat of a retrospective and what's currently going on with bacterial contamination of platelets. One thing this Committee ought to realize is that a lot of the innovation in bacterial testing of platelets came through this Committee over the years. A lot of the discussion had been right in this Committee.

Conflict of interest, we usually say that there's a company out there that hasn't supported my lab. See me after this talk. You've all seen variations on this slide about the viral risk of transfusion and for a variety of reasons we've done a wonderful job with viruses but bacteria was hanging in at around 1 in 1,000 to 1 in 2,000 units being bacterially contaminated for years and we just sort of didn't look at that. And finally it sort of rose to the top and has been of great interest to the blood banking industry for the last couple of years.

So, first I think we need to stop and look at, you know, where do these platelets come from. And of course there are two types of platelets. You can donate a unit of whole blood that's fractionated into plasma, red cells in a small bag of platelets which we tend to talk about as a random platelet, in a therapeutic dose is a pool of four of six of those, or you can hook someone up to an apheresis machine. As you see here, you see a happy, healthy donor hooked to a Fenwal CS-3000, one of the older machines, donating apheresis platelets. In fact, I liked this donor so much, I married her.

But you also, you see here the sources of bacteria. There are two, possibly three sources of bacteria getting into platelets. One is from the donor's skin, from the arms. When we do an arm prep we do not sterilize the skin. All we do is a bacterial load reduction. There are bacteria below the skin surface and the skin appendages where we do not reach in with the iodine-type solutions and a core comes up the needle into the tubing, into the bag and can still carry bacteria into the bag.

The second source is that people can have transient bacteremias and a lot of the bacteria that contaminate platelets and ultimately kill people are

the kind of bacteria that we normally have in our gut and people have transient bacteremias from that.

The third possibility, which is I think less well-understood, is that there is some data in the literature that suggests that some bacteria can come from outside the bag and make it into the bag, whether that is through micro-cracks in the bag or through some other mechanism that's poorly understood. That is a third possibility where bacteria is coming from.

In terms of the estimates, in the early part of this decade, roughly 4 million bags of platelets were being transfused around 2000, of which 1 million were apheresis bags and 3 million were random bags. At the time we thought about 1 in 1,000, 1 in 2,000 were bacterially contaminated. We were handing out 2,000 to 4,000 bags with bacterially contaminated platelets in this country per year.

There are various estimates about what

percentage would result in clinical sepsis. Some people said it would as few as 1 in 10. Some data from the University Hospitals of Cleveland suggested that

almost 40 percent resulted in clinical sepsis but that was after they had screened out the most contaminated units with gram stains in their study. So it was probably a little higher. Nevertheless, this would have meant 200 to 1600 cases of clinical sepsis resulting from bacterially contaminated platelets in this country.

What percentage of those would have resulted in fatalities? And it depends on the organism. Gram negatives are much more dangerous than gram positives. And estimates vary from about maybe 1 in 5 to one in three across the board. So, we're talking about 40 to 533 deaths per year or a death rate, fatality rate of 1 in 7500 to 1 in 100,000 per unit of platelets.

Now, is there any validity to this

cascading set of assumptions? And the answer is yes. If you look to the literature, for example, data from Johns Hopkins, Paul Ness (phonetic) and his group found that with apheresis platelets the risk of death per unit was 1 in 17,000. For a -- I'm sorry, that was for

a pool of random platelets. For an apheresis platelet it was 1 in 61,000, and then data from the University Hospitals of Cleveland, from Tobian (phonetic), was roughly 1 in 50,000. So, the numbers support these kind of assumptions.

Over the years the FDA sponsored several meetings to try to deal with this problem of bacterial contamination. In 1999, there was a meeting and it was summarized by Ed Snyder. Ed Snyder is the blood banker at Yale. There is a picture of him here. He looks a little older now. But what he concluded in the final statements, in the final summary statements of this meeting was that what he was hearing at this meeting was that the imperative was to act so we don't have to explain ourselves to Nightline, "Why aren't we doing something about bacteria contamination of platelets?" And the feeling was regulation was necessary to achieve the goals. "Nothing says I care like a page of 483s." These are the deficiencies that the FDA hands out, as Jay knows. And, "When all else fails, do something. Give us a mandate and we will do the rest." And so

what the blood banking industry was saying is we can't get our hospital administrators to back us up to allow us to do something unless somebody allows us we have to do it. And unfortunately that was not forthcoming for awhile.

In 2002 several things changed. The first thing was the BacT/ALERT, automated liquid culture system, which is being used in a lot of clinical microlabs around the world, was validated for quality control of platelets and cleared by the FDA for QC. Subsequently it was one of these mergers that we heard about, bought by "BioNayro." Actually, much of the validation data through the years has come through my lab.

Also in 2002 a second quality control system was approved by the FDA. This was the Pall bacterial detection system that looks, I guess I should say that this looks at the production of CO2 in the bottles and has a colorimetric sensor at the bottom. This system uses a little pouch that looks at the PO2 being consumed in a bag. So it looks at the PO2 in the

head space. And it actually in some ways grew out of some experiments we did in my lab back in the early nineties. So, it's kind of interesting to see what happens when you publish something and you don't apply for a patent.

This has evolved into a second-generation system which is the Pall eBDS. I used to say you couldn't buy a Pall product unless it had a filter in it. They proved me wrong. They took the filter out, because the filter actually took out about 50 percent of the bacteria, and that was a bad thing for the bacterial detection system.

And the other thing that happened in 2002 was that we had a third FDA-sponsored meeting dealing with bacterial contamination of platelets and although the emphasis was on pathogen reduction, at the end of the meeting a group of the speakers and moderators got together and issued this open letter to the blood blanking community. I used to think that you write these open letters, someone reads them you just sort of file them away in the trash can but this seemed to be

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tipping point for bacterial contamination in this country. And this was signed by Jim Aubashon from Dartmouth, R. Tobian (phonetic), University Hospitals of Cleveland, Moe Blackman, McMasters, Paul Ness of Hopkins and myself.

And this said that pathogen reduction is not going to happen anytime soon in the United States. We have a problem with bacterial contamination of platelets. We have possible solutions with culturing. We need to start doing things. And, this really was the tipping point although at least in one circle somebody accused us of blackmailing the blood banking industry. I thought that was an interesting response.

This led to the AABB, American Association of Blood Banks, and the CAP, the College of American Pathology, to change their accreditation standards. Now, these are two voluntary accredited agencies in this country that cover the vast majority of blood banks and transfusion services. So, that the AABB said the blood bank or transfusion service shall have methods to limit and detect bacterial contamination in

all platelet components, and the CAP was, does the laboratory have a system to detect the presence of bacteria in the platelet components.

What many of you may not know is that there was concern about what the impact would be on the availability of platelets in this country if we began screening platelets. And sort of at the 11th hour, because the AABB standard was scheduled to go into effect in March of 2004, on February 24th, 2004, a letter went out from the Acting Assistant Director of Health, Christine Diato, to the AABB requesting that, "Because implementation may cause effects on the availability of platelets issue, we request that the AABB careful consider a delay in implementation." AABB responded, "After consideration of the issue, the AABB believes that further delay in implementation of this standard will compromise both patient care and the public health." And it actually happened. We'll talk about the impact in just a second.

So, there are several strategies that the country had followed to try to impact the risk of

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bacterial contamination of platelets, one of which is looking at arm-preps, which in the interest of time I'm not going discuss specifically. The second was a possibility of shifting the supply more toward single donor apheresis platelets. Paul Ness at Johns Hopkins looked at this in some detail. And during the eighties and nineties they had a conscious effort to shift from pools of these small bags of random platelets to single donor apheresis platelets.

So, in 1986, 48 percent of their supply of platelets was pooled random platelets but by 1998 they had gotten their percentage up to 99.4 percent. And during this time their reaction rate fell at Johns Hopkins, which transfuses probably more platelets than any other single institution in this country, because they have a very large oncology service in terms of apheresis platelets. But, the difference in reaction rate between a six-pack, six random platelets pulled together and an apheresis pack was a 5.4-fold difference, which is not what you would expect from six different products compared to one product, one

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needlestick versus six different needlesticks, one donor versus six different donors.

So, many people were moving in this direction. And if you look at the percentage of apheresis platelets transfused per year in this country, it's almost a straight line, so, that by 2004 by two different surveys, in 2004, roughly 80 percent of all platelets being handed out in this country were apheresis platelets. And it's estimated that the percentage is even higher now.

Now, Jim AuBuchon took this figure and extended it and he projected that by 2010 if we keep going at this rate 100 percent of all platelets in this country will be apheresis platelets. I think that's unlikely to happen. I think we will always have some random platelets but certainly the trend in this country has been to move to one donor platelet versus multiple donor platelets.

Another initiative was the diversion of the first couple of "mils," 15 to 30 "mils" of blood. And what this does is, probably the most contaminated blood

that is coming from the skin is in the first couple of "mils." And there have been data from France and from the Netherlands that suggest that perhaps 50 percent of the skin contaminants can be eliminated if you divert the first couple of "mils" of blood.

Now, as Tobian likes to say, one shouldn't be diverted by diversion. While it's true you can clear out a lot of these skin contaminants, when you look at the bugs that contaminate bags, roughly two-thirds are gram positive skin contaminants but if you look at the bugs that kill patients, roughly two-thirds of them are gram negative. So, they're not coming from the skin by and large. So, yes, you can knock down your contaminated units but you may not impact the number of fatalities too much.

Interestingly, you would think putting a little diversion bag on a blood collection system would be easy but it was fraught with lots of problems, both on the whole-blood bags as well as on the apheresis bags. And I have several slides that Richard Benjamin was kind enough to share with me from the Red Cross.

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And one of the problems that the Red Cross noted was that the two-arm apheresis procedures -- and you can either do a two-arm procedure or you can do a single-arm procedure -- had a higher bacterial contamination rate.

And when they looked closer at it, it was almost double. When they looked closer at it, they found that the diversion bag had been placed on the return line, not the draw line, the inlet line, so that presumably the plugs were coming up, contaminating the line. You want to get it out as fast as possible. And so the systems were reconfigured. This is actually the Baxter-Fenwal system, and it was moved to the in-line. And I was talking to Richard before that after they did this they have seen a drop in rate of bacterial contamination although multiple variables are at play. So, that's one of the initiatives that has been put in place in this country.

Now, what about the impact of culture? In 2004, in the spring 2004, there's an Inter-Organizational Task Force on Bacterial

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Contamination Platelets that tried to assess what the actual impact had been on the blood supply. And there were several questions that were asked. One was, has your ability to provide platelets been affected since 30 days after implementation of blood culture? And the vast majority of blood centers, hospital blood banks, and transfusion services, said there had been no change or little change in their ability to provide platelets to patients.

Another question was, are you currently experiencing increased platelet outdating? Because it was thought that if we held platelets longer while we did these culturing kind of tests, that they were going to get out older and then more likely they would outdate but the vast majority said that either there was no increase or a very small increase in the number of outdates. So, that didn't seem to be a problem.

We also looked at, were you using a culture-based method such as the BacT/ALERT or the eBDS, which I described before, or a non-culture method? Now, the way things played out, doing a culture method on a single donor apheresis platelet was logistically relatively simple, and the vast majority of apheresis platelets were tested using a culture method; however, application to random platelets, which initially at the time was that you were only allowed to pool them just a few hours before you were to transfuse them, was logistically difficult, expensive, and just the process was difficult to sample the bags. So, many people went to these non-cleared QC methods, surrogate methods, such as looking at pH of the bags or looking at the glucose because as the bacteria grew, the pH would drop and the glucose would be consumed in the bags. And, actually my lab was one of the first to describe that as was Steve Wagner's lab. We both sort of put it in the literature at about the same time.

Unfortunately, there's a big difference in the true positive rate. Initially here we're looking at about 1 in 4,000 were true positives versus the nonculture methods, 1 in 18,000. Why is that? Well, the answer is because the nonculture methods are not very sensitive and so you are missing a lot of cases that way. And, it was a mistake, I think, to even have allowed the nonculture methods to be used to screen.

So, what's the rate? The Red Cross has published now two papers on their experience. Their initial experience showed a true positive rate of about 1 in 5,000, which has pretty much held steady. When they looked at ten months before the implementation of culture versus ten months after, the high-probable septic transfusion reactions, they found a 75 percent drop in reported high-probability septic transfusion reactions. Now, subsequent follow-up over a longer period of time suggests that that may have been only now a 50 percent drop. But in any case we seem to have impacted significantly on septic transfusion reactions.

Now, even before we began culturing we knew that the older the platelet, the more dangerous the platelet was. And that's why platelets have a fixed shelf-life, and that even after culture we're still continuing to see this problem. Now, we know that fresh platelets, day-one platelets can also kill but largely it's the older platelets. And from the Red

Cross data, from Eder, et al., published last year in Transfusion, the majority of septic reactions occurred on day five platelets, in all the fatalities, the three fatalities that were reported to the Red Cross. So, that remains a problem and it remains a concern, particularly, as we're going to get to in a minute, the extension of the shelf-life of platelets.

However, across the board, I think we can say we've had a success. Again data from the Red Cross, before culture they had 12 reactions and two fatalities so that the transfusion reaction rate was 1 in 40,000. After culture, dropped 1 in 75,000 and after they got their diversion straightened out, most recently it's been running about 1 in 175,000. They've had one fatality during this period, October 2006 through October 2007, so that the fatality rate at least as has been reported back to the Red Cross, which, no question, is probably underreporting, but it's currently running at 1 in 700,000. So, I think that that's a success.

Other centers in North America -- and I've tried to limit most of my talk to North American experience. This is Hema-Quebec. They put several interventions in place, such as apheresis pouches, culturing of all their platelets. This was an abstract presented at AABB in 2006, and what they found in it is they don't see any more cases of sepsis being reported back to the blood centers in Quebec. And Blood Systems also had that experience. Since they began culturing they have not had any cases reported back to them. So, we seem to have impacted the cases.

What about the use of the BacT/ALERT system? You can either use one bottle or two, one being an aerobic bottle, versus, and then other being an anaerobic bottle. Most people started with an aerobic bottle. This is combined data from the Red Cross, published data from the Red Cross and Blood Systems looking at roughly 1 and a quarter million platelets, 207 true positive isolates. Of these 206 were interdicted; the units did not get transfused to the patients. Again, I consider that largely a success. Many of these are gram-negative organisms that in all likelihood would have killed patients.

What about missing cases? Are we missing cases? If we look at the BacT/ALERT system, there was a study done at UNC, at my institution. We looked at roughly 2400 apheresis platelets that were sampled on day two and then again when they were issued or when they outdated, in no case did an issue or outdate culture detect contamination that was not detected on the day two culture. The numbers are small but this at least initially sounded promising.

For the eBDS, their positive rate, looking at 118,000 apheresis and whole blood platelet concentrates from 23 blood centers was running a true positive rate of about also 1 in 5,000. Their false positive rate is a little higher than that which has been reported with a single bottle, BacT/ALERT, but not too bad. And in this study they reported one missed case of staph epi, that caused a transfusion reaction. Staph epi is a slow-grower and it is expected there would be some slow-growers that would miss an early culture.

In terms of specificity, this is data from Canada, Gail Rock, looking at the first generation of eBDS coming from donor to patient who is being transfused. They sampled 12,000 random platelets and then again when they were pooled and sent out to be transfused, they found they had missed one unit. So missing 1 in 12,000, so again, that sounded promising. Oh, this is just to show you that the blood is dripping.

Okay. Now, one of the initiatives that has come out of all this and was worked out to a large extent in this Committee and other places was that there was a desire to go back to seven-day storage of platelets. Platelets were stored for seven days in '86, pretty much to everyone's satisfaction. The efficacy and the survival was thought to be adequate but because of fear of bacterial overgrowth over time it was brought back down to five days. So, a postmarket surveillance study called the Passport study was initiated in 2005. And New York Blood Center was the first to go with this and it involves both Gambro

and Fenwal platelets.

Primary hypothesis is that 7-day single donor platelets would be no more dangerous than a 5-day untested platelet, in a nutshell. What this means is that we're going to have about 50,000 outdated platelets that are going to have to be repeat tested to see if we meet this number. There are 29 organizations involved, 47 centers. Accrual has been slow but there have been 193,000 platelets that have been tested up front -- consider that tier one testing. Tier two testing has been slower. There have only been roughly 2600 platelets tested at outdate. Remember, we have to get to 50,000 so it's going to be awhile. But, I think worrisome is that of these 2600 tested platelets, two of them are positive. So, that's roughly 1 in 1300 are missed by an earlier culture. Now, this may be a physical anomaly. Only having two positives is a small number but it's something that's concerning that we're going to have to keep a close eye on. Both were staph. One was a staph aureus, the other was a staph epi. What does having 7-day platelets do for you? This is

data from UNC, from my lab. One thing that happens is you have a shift in the age of platelets. Platelets tend to be a day older but at least in our experience only about 8 percent of platelets are transfused on day six or seven so it's not a lot of your inventory that are beyond day five.

And practically what it did for us, it meant that we had an additional, I think it was 320 platelets available that year and in terms of acquisitions, because we would have had to have gotten those platelets from outside of our own blood center, we may not have gotten them.

And, so, I think with having seven days is it provides more platelets in your inventory so you can serve your patients better. And generally what most people's experience has been is that your outdate rate drops about 50 percent. Actually, in our experience it was closer to 60 percent. So, that's significant. It also pays for all the testing. In terms of the acquisition costs, it would easily pay for all the bacterial culture testing that we were doing. So,

there is at least one school of thought that is very pro 7-day platelets. It's one of the few infectious disease tests that have been put in place that actually makes the blood supply safer but saves us money. And so that's very unusual.

There are couple other issues I want to just quickly hit on. One is that we really don't know what to do about anaerobic cultures in terms of the significance. Clearly anaerobic organisms can cause sepsis and fatalities. There have been reports in the literature of platelets and red cells, with clostridium. This is an interesting report. It is thought that the young donor, he was a young father, he often changed his little baby's diapers by holding his baby in the crook of his arm. While he was changing the, quote, "Nappies" -- this happened in England -- and it was thought that the clostridium came from the stool on his antecubital fossa.

Other cases reported to the FDA over the last couple years have been a couple anaerobes, two Clostridium, one from red cells, one platelets and a

U-bacterium, so, plus anaerobic organisms can cause sepsis. And, so, there has been a concern that we need to look at anaerobic cultures.

Other arguments for the use of an anaerobic culture, one of which is that it is a different media and some bacteria like growing in a different media versus another media. So, in addition to the PO2, the oxygen detention in the bottles, it may just be that the media does make a difference. With a couple streps, in vitro experiments, you can get much more rapid pickup, 43 hours versus 21 hours, aerobic versus anaerobe for a strep-varidance; however, this has not really translated into any clinical impact as yet. We don't know of any cases where a unit would have been interdicted had we had an anaerobic bottle versus an aerobic bottle just because of the time difference.

We also know that some organisms grow differently when there are very few organisms in the bottle. This is looking at increasing organisms in a bottle. And this is with the anaerobic bottle. This is with an aerobic bottle. This is with a

coagulase-negative staph lugdunensis, very little organisms, the rate is also much faster. So funny things happen when you only have a few organisms that make it into the bottle.

Nevertheless, despite all the good things that I've been saying, we do see cases slipping through. This is the mMWR from CDC, February 2005, describes several cases that have slipped through and caused sepsis, including that staph lugdunensis which I showed on the graph just a second ago.

And then despite the best-laid plans, other things happen. This is a death in Kansas City, with E. coli. The BacT/ALERT machine detected this E. coli, over the weekend. Unfortunately, the computer interfaced going from the BacT/ALERT to the blood center's computer was down and no one realized it. There is an audible alarm on this machine. They had turned it off. There is a visual color change on the screen of the BacT/ALERT. Well, it was sitting in a back room with the door closed and nobody looked at it. And when they walked in Monday morning and they saw the

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alarm flashing, they called the hospital and they had just missed calling back, that unit was transfused and the patient died. So, no matter what you do, this case can still happen.

What about pooling of random platelets? In 2005, Pall Corporation introduced the "Acrodos" pooling system so now we can take the Pall random platelets, pre-pool them, keep the entire shelf-life for five days, which facilitated the use of a culture, which was a good thing. And most recently in 2007 this was extended to all the other approved random platelets that are available in the U.S. Unfortunately, the penetration of this in the market has not been as great as I would have liked to have seen.

Finally -- well, not quite finally -- almost finally, there has been a lot of interest in rapid testing done closer to the time of transfusion so you can try to pick up these cases that are slipping through. This was discussed in the BPAC meeting in March 2006. One of these, which has already been discussed here today, is the Virax Pangenera detection

system which is basically a lateral flow device -- it's similar to a urine pregnancy test -- that will detect bacteria but it's only picking up ten to the fourth to ten to the fifth organisms per mil, which is not as great a sensitivity as many of us had hoped for these rapid tests but it was the first to come on the market and it was licensed as adjunct test to an early culture for apheresis platelets, probably not where we needed it the most but for marketing reasons they thought that was the easiest way to go initially. It's currently being distributed by Abbott.

What's going on in the rest of the world? Many countries have gone to 100 percent bacterial screening. Denmark, Ireland, Netherlands, Norway are just are few examples. And they use this to go to day seven of storage. Some countries, like the United Kingdom, they'll only use it over long weekends, to extend it seven days. They'll test on day-three and then bless it through day seven at least for outdating purposes. Other countries have continued to just use BacT/ALERT for QC testing so a small percentage, often

5 percent, are used, such as Austria and Germany. France, which is probably the only other country that has such a high use of apheresis platelets, as we do in this country, has been going back and forth about what is the best thing to do and they have decided to use a gradual implementation of pathogen reduction. And

we've already heard about the chikungunya virus -- if I can say that right -- which was actually implemented on -- oh, I'm going to get this wrong, too -- La Reunion Island, is that close -- in the Indian Ocean, and France has decided to slowly implement pathogen reduction throughout the French system and they're going to be starting with Guadeloupe and Martinique in the Caribbean Islands. So, I'm sure we will hear more about that later in this meeting. Japan, interestingly enough, only keeps their platelets for 72 hours and says that, "We don't have much of a problem." And they may be correct because they're fresher platelets but they have had at least two deaths from bacterially contaminated platelets in the last seven years.

Finally, there's a lot of things about

bacteria that we just don't understand. This was a study from the NIH Clinical Center from the early seventies, where the clinical microlab noticed that there were a lot of Salmonella choleae-suis cases. They did an epidemiologic search and what they found was that all these patients had received platelets. When they looked closer, they had all received platelets from the same donor. All these platelets were one day old or less, which was the licensure of apheresis platelets at the time, but the time from when they got that platelet or received that platelet until they became sick was on average 8.6 days and by that time, you know, people had forgotten that they had even given these patients platelets. And so there are a lot of things going on that we don't understand. And there was one death directly from Salmonella choleae-suis and two or three cases of recurrences due to this.

Similarly, in the last two years there was a heparin flush on a catheter sip that was found to be contaminated with Pseudomonas fluorescens and it was recalled. A follow-up of patients who had received

this heparin flush identified 15 patients in Michigan, 13 in South Dakota who had a delayed onset of Pseudomonis fluorescens. And this occurred from 84 to

421 days after their last potential exposure to the contaminated flush.

And I think this stresses that we don't really understand everything about bacteria. Bacteria can go in at low levels, can seed the body or artificial surface somewhere and then show up in these cases over a year later. And, I challenge anyone to think about a platelet that they transfused a year before.

Okay. When I was preparing this talk, I looked back. There were several talks I had given over the years and I noticed that there were several things that we were hoping for years ago. One was seven-day apheresis platelets. Well, we have them. Prepooled random platelets, we now have them. New approved rapid detection systems, we have the first one now. So, I think we have been making a lot of progress. Maybe we could do a little bit better. Maybe pathogen reduction

might be an improvement but I'm going to leave that to be debated by the next couple speakers. I've sort of been in the center of the storm about bacterial contamination of platelets. Sometimes I feel like I have been a lightning rod. So I think that this is sort of me and I've awoken the sleeping bear. I think we have some time for a question or two.

DR. BRACEY: Thank you very much, Mark, for the extensive review and great information. We have time for one or two questions or comments from the Committee. Okay. Dr. Klein and then --

DR. KLEIN: Thank you, Mark. Mark, how do you know that your false positives are really false positives?

DR. BRECHER: Well, we don't. That's a good point. For example, it may be that the bacteria has died out in of bottle. And, so, actually, I was discussing this with Mike Busch before, that if you're going to call something a false positive you shouldn't base it just on a negative subculture of the bottle. You should, I think, at least do a gram stain because even if the bacteria has grown in the bottle and died out, you will still see that on a gram stain. We've seen that with Bacillus cereus in the bottles. And, so, I think there is a problem in the way we're doing things. Maybe we need to have a little get-together of all the big parties and figure out what the best way is of quantifying these risks.

DR. BRACEY: Dr. Benjamin?

DR. BENJAMIN: Dr. Brecher, thank you for a great summary and showing off my slides.

DR. BRECHER: They were good slides. Thank you. You can use mine in the future.

DR. BENJAMIN: Thank you. I will. I had a question about the Passport study. You mentioned the success with seven-day platelet and how we've seen a reduction in outdates and a saving for the hospital and the transfusion centers. Yet, it does appear that the day six and seven platelets are at increased risk for these patients. I was wondering, the clinical study being performed for publication and for licensure -- I think of the as a release test -- is being performed without patient consent or IRB approval and appears to be generating increased risk to patients. Do you have a problem with that?

DR. BRECHER: Well, personally I don't. This a postmarketing surveillance study. Just like any other postmarketing drug test, you generally don't get informed consent. So I don't -- and actually we ran this by our IRB in my institution and they felt that it did not need informed consent as it happens.

DR. BENJAMIN: Were they aware of the data suggesting increased risk?

DR. BRECHER: I think they were aware in a general sense that the older a platelet is the greater the risk there would be bacterial overgrowth. That's one argument. On the other hand, would you rather not give them any platelet at all? Because often you're out of platelets and what's the better solution, to give them a day six or seven platelet or no platelet?

DR. BENJAMIN: I guess the question there is, are these older platelets being used only in that circumstance or are they being used just for inventory control in order to save money for the hospital when there's a plentiful supply?

DR. BRECHER: Well, I think there's probably variability. Jim AuBuchon, for example, of Dartmouth uses it just in that setting but I think most people are using it to pay for the testing and to increase their inventory. I think, you know, having, in my case, you know, we're having an additional almost 10 percent platelets in our inventory. That has impacted. We're rarely running out of platelets now.

DR. BRACEY: I think in the interest of time we need to move on to our next speaker, who is Dr. David Asher. Dr. Asher is a graduate of Harvard College and Medical School. He's a diplomate of The American Board of Pediatrics. Dr. Asher is the Chief and Supervisory Medical Officer of the Laboratory of Bacterial, Parasitic and Unconventional Agents and he will speak to us about unconventional agents in that he has great expertise in TSEs and he will present a talk entitled the Development of Tests for Variant Creutzfeldt-Jakob disease. Welcome.

DR. ASHER: Thank you, Dr. Bracey. Dr. Holmberg, thank you for inviting me. First some housekeeping. A brief disclaimer, I'm going to try and summarize information relevant to TSEs and I do work for the FDA; however, this is not an FDA-cleared talk. As usual, I'll attempt to say nothing offensive to senior management of the agency but you never know what is going to happen, except for two quotations, everything in the presentation has been available in the public domain and primary sources should be cited if you want to site anything official, a CBER Web site and particularly the WHO guidelines on tissue infectivity, both of which as well as primary research sources are cited in the handouts which the folks at the table are supposed to have gotten. And I made some more for the audience until I succeeded in burning out something very important in our copier, for which the rest of our staff has not yet forgiven me.

I'll start with a brief introduction to the TSEs but I'm going to have to assume that most of you at least at that table know a considerable amount about them, and their pathogenesis, particularly those aspects of the pathogenesis relative to blood safety. Then I will discuss variant CJD, mainly food-borne but not known to be blood-borne as well, recent transfusion-transmitted cases. I'll provide information in the handout on FDA donor deferral policies that should reduce that risk but I won't summarize them in the talk, and then I will turn to what Jerry asked me to address, which was the prospects for antemortem tests for detecting spongiform encephalopathies during life, theoretical prospects for infectivity assays and those tests in development that have been claimed to show promise, most of which are based on detection of the abnormal prion proteins that are associated with the diseases. And I will close with a brief reference to some surrogate blood tests which have not yet delivered on their promise, and the need for reference materials.

I will say that, although I see that Celia Witten from our Office of Cellular and Tissue Products has departed, that as far as tissue donors are

concerned, where a postmortem test would be effective, there are many such tests that are already licensed for animal use, nine of them in the European Union, and I see no reason why if it were decided to develop such tests because autopsies are being done to retain postmortem tissues, why those tests wouldn't be immediately relevant to human tissue and organ donors.

First, the introduction, TSEs are a terrible group of diseases that can turn a brain that ought to look like the one in the top row into something spongy-like in the second row. A large number of other abnormal findings, the most important of which are the formation in brain tissues and sometimes in other tissues of the amorphous-stained material that you can see in the far right row. These are called amyloid plaques in the brain.

There are four or five TSEs of animals depending on how you want to split them, of which all except feline spongiform encephalopathy have been seen in the United States and because of its demonstrated blood risk, variant CJD is the most important to us

today. In the United States, BSE remains very rare, though it has occurred. Transmissible mink encephalopathy has not been seen here since 1983. Chronic wasting disease in deer, elk and moose, is spreading widely and we have had scrapie in the country since the mid-1940s.

Except for BSE, none of these animal diseases have been implicated in human infection although monkeys are susceptible to experimental infection with all of them so there certainly is no absolute primate species barrier. The human TSEs, so-called prion diseases, three to eight of them, depending on how you want to split them. Kuru teaches a lesson for public health and demonstrates that the incubation period for infection can approach 50 years. Creutzfeldt-Jakob disease has been known since the 1920s, and variant Creutzfeldt-Jakob disease, the first case became known in 1994 and described in 1996. The two at the bottom are extremely rare and I'm not going discuss them.

All these diseases are known to be

transmitted, can be either food-borne or spread by products and unfortunately some of these products are in classes regulated by the Food and Drug Administration, surgical instruments, small number of corneas and a very large number of dura mater allografts and human cadaveric pituitary hormones that are no longer approved products in the United States. Of concern today are the four transfusion-transmitted cases reported from the UK, the first new class of medical product implicated during the past ten years.

I want to mention kuru just because -- and some of you have heard me say it before -- I think it provides a very important lesson for regulators and product manufacturers. In 1957 kuru was the leading cause of death among women of the Fore language group in Okapa, New Guinea. In 1957, not for medical reasons but for aesthetic reasons because it violated Australian and Queensland law -- they were the occupying government -- the practice of ritual cannibalism was prohibited. Over the next 20 years, the cases of kuru fell to almost nothing. In 1999,

there were no cases at all. And there was a case in 2003; mosts years no cases at all. There's no cure for kuru. There's no vaccine but simply preventing contact with contaminated tissue appears to have eliminated completely an epidemic of the spongiform encephalopathy, something for us to keep in mind in protecting the safety of tissues and blood.

I don't have time to talk in any detail about the pathogenesis of the spongiform encephalopathies. These have been well-summarized in a WHO document by a working group which will continue to meet periodically to keep it up-to-date. And I have broken the table in the document down into several slides, one which is missing some of the reprints so I stuck it on the back.

Red indicates tissues in which either infectivity or abnormal prion protein has been detected. A question mark means there are results that are not generally accepted and the other colors show that either tissue has not been tested or has tested negative.

Most CNS tissues contain substantial amounts of transmissible material and abnormal prion protein in all models tested. Some of them were spotty results with lymphoid tissues and tissues of the intestinal tract. You'll notice at the very bottom that in blood of human beings, infectivity has been detected in variant CJD but only by the natural unfortunate transfusion-transmissions attempts to demonstrate infectivity in experimental systems have not yet been successful although there's no reason to doubt that infectivity is there.

And attempts to demonstrate prion proteins have been equivocal, some laboratories claiming success, others not accepting them. Many tissues that have been tested had no detectable infectivity; however, keep in mind that all negative attempts have severe limitations, small numbers of cases studied, small volumes, limited sensitivity of the assays used and the uncertain relevance of the animal models to the human diseases.

The CDC pulled together ten years ago the

published epidemiological studies looking at exposures of CJD patients to blood to see whether blood constituted a demonstrable risk factor. Seven studies were very reassuring and remain reassuring for previously known forms of Creutzfeldt-Jakob disease; however, the animal studies were not reassuring at all. A number of animal models demonstrated consistently that infectivity could be found in blood, and then the cases from the United Kingdom demonstrated without much doubt that it was occurring with variant Creutzfeldt-Jakob disease.

Most of what we know about the dynamics of infectivity in blood comes from the work of Robert Rohwer of the University of Maryland in the early years together with Paul Brown of the NIH and more recently with Louisa McGory of the University of Maryland. The first demonstration of infected blood was from Elias Emmanouilides and Laura Emmanouilides. Laura is a member now of our TSE Advisory Committee, who found infectivity in the blood in guinea pigs experimentally infected with brain materials from humans with

Creutzfeldt-Jakob disease and those findings were subsequently confirmed in a variety of other animals though not all models have been positive.

The amount of infectivity demonstrated by intracerebral inoculation of hamsters in hamster blood was relatively low, anywhere from 2 to 27 infectious doses per milliliter, which would be very difficult to demonstrate by any test but more than enough to infect a recipient if a large volume is delivered by the intravenous route. The infectivity appeared about halfway through the hamster incubation period and continued to rise into clinical disease, never dropping. Keep that in mind later in the talk when I review for you the findings of some of the tests for prion protein in blood.

The distribution of infectivity in blood components was interesting. It was found in all the components but there is some evidence that intrinsic infectivity is restricted to the nucleated cells and to plasma but, of course, all the components have some degree of contamination at least with plasma.

So, now let's turn to the risk of BSE which, is the presumed origin of variant Creutzfeldt-Jakob disease. First in North America we have had three recognized cases in the United States, one of them from Canada. Canada has had at least 12 recognized cases, 11 native and one imported from the UK in 1993. The UK has had the great majority of cases worldwide. Cases peaked there in 1992 with just under

40,000 diagnosed cases. No one knows, of course, how many truly infected cattle there were but the exposure of the population in the United Kingdom to contaminated beef products must have been considerable.

A total of 25 countries have reported BSE in native cattle following feed bans and other protections put into place in the United Kingdom. The number of diagnosed cases there has fallen sharply. They had 114 cases down from that peak of almost 40,000, 114 diagnosed cases in 2006, and only 49 cases through the 30th of September of last year. If you will notice, the OIE comparison of the reported incidence in 2005 shows that in the United States and

even Canada appears to be considerably less than those in the BSE countries of Europe. Portugal reached 53 cases per million adult cows defined as over the age of 24 months. Of course we don't pick up all the cases, we know that, neither do the European countries, and the conclusion must be that the prevalence of the disease in our country still appears to be considerably lower than it is in the countries of Europe.

Unfortunately, there's another risk of BSE throughout the world and that's posed by the widespread export of contaminated meat and bone meal from the United Kingdom. During the worst years of the outbreak, we imported some, Canada imported some. Although there's no record of the import, they have records of the export.

And a number of countries that have not recognized BSE have records of importing that contaminated material. We don't know what they did with it but the assumption has to be that they might have unreported cases of BSE. There's no reason to think that their contaminated products would have any

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less potential for infecting people than UK products themselves. So, that there's a worldwide risk. We hope it's low. We don't know what it is.

There's very little reason to doubt that BSE is the cause of variant CJD. The disease, I can't summarize the condition for you but it had unique clinical presentation, unique pathology, the so-called florid plaques that you can see on the left surrounded by halos of vacuoles and a striking accumulation of prion protein in lymphoid tissues that are not seen in other forms of CJD.

There's some difference in the magnetic resonance imaging. I won't go over that. Sporadic CJD tends to have hyperintensity in the interior regions, the basal ganglia, whereas variant CJD, further posterior, although in individual cases this may not be helpful. A total of 204 cases reported through December of last year, 166 of them in the United kingdom, 38 nonUK cases of which at least 7 were probably infected in the United Kingdom, 6 of the patients having lived there for more than six months,

including two of our three cases and the case in Canada.

Our third case was in a recent arrival from Saudi Arabia, which has not recognized a BSE case although neighboring Oman had an imported case and there has been a variant CJD case in Saudi Arabia itself. It's interesting that all these people would have been deferred by current FDA-recommended policies except for the one case from Saudi Arabia, have not been in the UK. Cases peaked in the UK in about the year 2000, that is, about 7, 8 years after the peak of BSE cases but in 2003 the first of four reported transfusion-transmitted cases were reported; vCJD donors, that is, donors later recognized to have vCJD in the United Kingdom are followed through the transfusion medicine epidemiological review.

There were 18 of them, 66 labile components distributed to 66 recipients; 23 of those recipients are still alive and of a very small number of recipients to survive five years, four of them have evidence of infections with CJD. Reassuring today, 174

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batches of implicated plasma derivative prepared and although recipients have been warned, there has been no report of variant CJD in any recipient in the UK of a human-plasma derived product and those recipients are being followed.

It's interesting that all four of the transfusion-transmitted cases seem to come from three donors and the component implicated were nonleukoreduced red blood cells but it seems too early in the game to conclude that leukoreduction was protective.

Food-borne cases, the cases from left of the UK give some evidence of what the incubation periods might be, somewhere between 9 and 21 years. The most interesting case is probably the Japanese case, came down 12 years after a 24-day stay in the United Kingdom, as close to a point exposure as one can expect. Although there are cases of BSE in Japan, they appeared much later than those in the United Kingdom.

The transfusion-transmitted cases, incubation periods can be set and those varied from

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just over six years to eight and a half years. The patient with evidence of infection but no clinical case died of an aneurysm five years after the transfusion. So, the incubation period is not that much shorter than seen in food-borne variant CJD. We hope that means that the dose in the unit was small but we really don't know.

As Roger Dodd mentioned this morning, striking difference between what's seen with Creutzfeldt-Jakob disease where he, Peter Page and Marian Sullivan have followed over a hundred long-term survivors of transfusions of blood from donors who later came down with Creutzfeldt-Jakob disease; none of those patients have evidence, have ever been had evidence of Creutzfeldt-Jakob disease.

So, the risk seems to be unmeasurable to date for sporadic Creutzfeldt-Jakob disease but substantial for recipients, at least of red cells from donors with variant Creutzfeldt-Jakob disease. We still believe that there is some theoretical risk because the finding of agent in blood is so consistent with animals it's hard to believe that with the human pathogenesis of sporadic CJD there can be that much difference.

Decisions about managing the risk, if you're not going to accept the risk, you can limit sources of raw materials to the safest possible history, which we're doing now, screening test which we're going to discuss, using manufacturing processes to reduce the risk, which seemed likely to be in play for plasma derivatives, less likely for labile blood components or restrict use of the products, which for blood products except for ordinary good medical practice is probably not a feasible public health option.

Stephen Anderson and Hon (phonetic) Yang have done a thorough risk assessment for plasma, plasma derivatives and variant CJD, some of which would be relevant to estimating the risk from labile components, and when they did a sensitivity analysis, the three most important determinants of risk are the clearance during manufacture and the quantity of product used by the patient, which we really can't control, or the prevalence of vCJD. And the prevalence of vCJD in the U.S. donor population is largely controlled by the prevalence of vCJD in the United Kingdom because it's likely that most of our infected donors, if any, will have been infected in the UK or from UK products.

Now, there's a problem in that it's not been possible to estimate the prevalence of people incubating variant Creutzfeldt-Jakob disease in the United Kingdom. I better skip ahead, but, based on a prion protein tissue survey, one estimate was that as many as 237 people per million might be infected whereas a model based on actual observed cases was towards a magnitude lower than that and we really don't know.

The fact that we have not seen a second wave of variant CJD cases is reassuring but it's probably early days considering the long incubation periods seen with other spongiform encephalopathies. So, that at the moment our policies to protect recipients are based entirely on deferral policies and are summarized in the handout our policies which we began in the late 1980's to reduce the risk of having people with incubating Creutzfeldt-Jakobs disease and particularly variant Creutzfeldt-Jakob disease in the donor population. The problem with a policy based on deferrals only is that most of the deferred donors are not infected and not all the potentially infected donors have been deferred.

The two possible solutions that we can imagine for that is one can introduce a process that would remove some of the infectivity, and at least two reports have suggested that certain ligands might be able to do that combined with filter technology. I think that that remains a very useful approach to consider.

And then the second one to consider for the rest of this talk is to develop validated reliable screening tests, presumably with confirmatory tests to detect infected donors and reassure them or even possibly reenter them. Unfortunately, there is no FDA-approved or licensed test for antemortem diagnosis or license for donor screening nor is there a pathogen reduction technique that's been reviewed by the agency. We encourage continued development.

Now let's turn to testing. The gold standard for TSEs has been and probably still remains detection of infectivity. In principle there are some cell lines that are susceptible to infection with some TSE agents. Unfortunately, they are very restricted in their susceptibility and human CJD strains and BSE strains have not been adapted to cell culture assays. The cells often lose their susceptibility. They have to be recloned. They're usually much less sensitive than animal assays. They require a considerable amount of technical expertise, a lot more than taking care of animals, and the animal alone may make at least three weeks, usually longer to read out so you don't save that much time there and the cells show no cytopathic effects so you have to do some sort of additional testing to confirm they've been infected anyhow.

There are a number of animal assays of which the most accessible appears to be in transgenic mice. I won't discuss the others. Unfortunately, there have been problems with transgenic mice for assessing human TSE infectivity, the most striking, which is probably due to a spontaneous disease that appears in mice that overexpress either mutant or wild-type prion proteins and they can be very confusing so that people interpret the acceleration of their disease, which is not an infectious process, with demonstrating infectious agent.

And, the second is false negative assays. I'll show you, if I get that far, I'll show you an example of that later in the talk. Some of "Prnp-transgenic" mice have been much less sensitive, sometimes relatively insensitive to variant Creutzfeldt-Jakob disease than you would have predicted by the engineered sequence.

I'll skip this slide. It just demonstrated that for ten years the results with an engineered line of mice suggested that there was de novo generated infectivity where in fact there was none.

So, the feasible tests have all been based

on the demonstration of this TSE amyloid that I shared with you at the beginning of the talk, found in all the spongiform encephalopathies. This was first demonstrated in 1981 in electromicroscopy, by Pat Merz and the following year by Stan Kruzner and David Bolton. Stan, of course, won the Nobel Prize for his very important work with demonstrating prion protein and its effects on susceptibility of the incubation period for the spongiform encephalopathies.

The workhorse assay has been the Western Blot. If these proteins, which are insoluble, the abnormal ones are unsoluable in detergent saline solutions and they're relatively insensitive to digestion with proteinase K and if you do those things and you can find a detectable band of the right size after you PK digest -- this light doesn't want to go on -- but over in the far left after you've digested with proteinase K the band remains.

The nomenclature of the abnormal prion proteins becomes so complex that ordinary human beings are really unable to follow it so that in 2005, in the

same document that I showed you, the World Health Organization, suggested a simplified provisional nomenclature in which all the forms of abnormal prion protein whether classified by their solubility or their PK resistance or the size of their fragments on electrophoresis, is they all be called PrPTSE. And there are additional names you could give to them if you wanted but those of us who can't keep it straight would be able to call them all PrPTSE.

Prion protein is a PPI-anchored cell surface protein. It's made up of about 253 amino acids. There are point mutations scattered along the backbone which are associated with familial CJD and there's 1 at 129, there is a normal polymorphism that's clearly associated with susceptibility to all forms of CJD but more strikingly with variant CJD. There's an association, as normal PrP, the normal precursor protein is transformed into abnormal PrP. It becomes largely beta-sheeted.

Stan Kruzner has believed strongly that this protein is the infectious agent and probably the

sole component of it. That is not universally accepted. Last year Laura Manulities reported finding the same abnormal tubular vesicular particles in infectious cell cultures that have been seen in multiple brains from animals and humans with these diseases. They don't fulfill Koch's postulates but neither do prion proteins. Here I summarized the properties of prion proteins but I'm going to have to skip those.

So, all the rapid tests used for animal testing and potentially for human testing have been based on the detection of the abnormal forms of the prion protein. And there are a number of factors that affect the sensitivity of detection, the amounts of agent tested, the proteolitic treatment, the denaturation of the protein, the affinities and specificities of the primary antibodies, the antibody labels used and most recently the amplification techniques and the co-factors which seem to affect that amplification and finally, little remarked on but very important in controlling variability robotics, those

laboratories that can afford robotics get much more consistent results than those of us who still have to do these tests by hand.

Other than electromicroscopy and Western Blot, a number of tests have been used to detect abnormal forms of the protein, particularly for screening ELISA variants, by immunohistochemistry, which is used to confirm positive ELISA tests for cattle testing. Dot blots aren't much used but there's one commercial strip test that's apparently doing pretty well in European cattle testing, a technique that I will go through very quickly called the conformation-dependent immunoassay, which uses an ELISA readout. And then the most interesting of the recent variants, the PMCA test and other tests called "seeding" assays which offers some opportunity for amplification of abnormal protein. And I will show you that in closing.

So, there's a Dot blot, immunohistochemistry, and in the same WHO document and repeated to some extent in an FDA, TSE Advisory

Committee Meeting, we invited six developers of candidate PrPTSE blood screening tests to present their early results. Six of them were presented in Geneva. I'VE summarized them on this slide, and the following slide. Some of them used proprietary ligands that seemed to bond with PrP and increase its detection, magnetic bead concentrations, a highly specific IGM that preferentially binds to abnormal PrP, a number of approaches of which the PMCA has attracted the most attention.

I must say that most of these tests, whether it's because they didn't develop very well or because of the market considerations that we just heard discussed, we never heard anything from again. Your guess is probably better than mine for why that is. For a while it was very difficult to get anything published as negative if you hadn't done a confirmation-dependent immuno-assay and although I will disclose that the developer of that test, Yuri Shakar, with Stan Kruzner is a good friend of mine, it is not currently being marketed in this country and I am not

sure that they're planning to continue to market it or to attempt to market it in Europe. It's much more complex to perform than other ELISA-based tests.

The basic principle of the test is to take native suspension and to treat it with hot guanidine. The native PrP is fully accessible without guanidine and the precipitated abnormal PrP is solublized by the guanadine. So, what is done in that test is you measure the amount of ELISA-detectable PrP in a native specimen and then you denature and measure how much additional PrP you can detect after guanadine denaturation. And you take a ratio and you do replicate specimens, and if the ratio is over some value plus a standard deviation, you interpret it as positive. And, the test appeared to be reasonably robust, which we defined as our guys being able to do it in a reasonable number of tries. It had a reasonable dose-response curve over two-fold log units, which is less than the literature described but, still, and it clearly could discriminate between infected and uninfected tissues.

The results in our hands -- we don't have robotics -- were quite variable. We tried to improve them by sonication but we thought of breaking up aggregate but that didn't help; it made it worse. The most disappointing thing for us was that it only appeared to increase the sensitivity over a standard, well-done Western Blot by about one log and it's an awful lot of work to improve sensitivity of detection. Now, it's true that ours are not optimized. We don't have robotics. We didn't develop the test but I am informed that other laboratories have had not dissimilar results.

The final test -- and this is what was responsible for 10 of the over 400 abstracts in a recent worldwide meeting attended by Pedro Piccardo from our group -- over ten laboratories reported variants of this so-called Protein Misfolding Cyclic Amplification or PMCA test developed by Claudio Soto and his colleagues, first reported in 2001.

In this technique small amounts of abnormal prion protein are incubated with an excess of normal

PrP in a cyclic process consisting of repetitive brief sonications and incubations and they provide the PrPC by adding suspensions of fresh normal brain. And you have to do this every 20 to 40 sonications or else the process, whatever it is, seems to get exhausted. This kind of "seeding" assay was first developed by Byron Caughey at the Rocky Mountain Laboratories but Claudio

Soto has really developed it to the state in which it is today. They conceive of this as taking fibrills of this abnormal protein, adding them to molecules of normal protein, breaking up the fibrills, and whatever their abnormal state is, they apparently attach to the normal protein and catalyze its growing into more abnormal protein.

This is all, of course, a theoretical construct but at least to a limited extent it does seem to work. So, they take infected brain, do a 1 in 10 dilution, add normal brain and then they sonicate it and incubate it and then they do it again and again and again and finally they do a Western Blot, although you can do an ELISA or a CDI or any other readout that you

care to adapt to it but they use Western Blot and most people do.

So, if you see this control, uninfected specimen in 40 cycles you go in an infected specimen from undetectable to this nice band of abnormal prion protein and in the controls -- ignore this little smear down there -- you don't. So, the steps involved are a sonication and an incubation. And this is a typical PMCA round, single-reaction depth in our lab trying as best we can to, as Claudio Soto described, 20 seconds of sonication, 10 minutes of incubation, and that's done 45 alternating times, at 75 percent of the sonicator's power; 37 degrees takes about eight hours.

And just as Soto described, we found the same thing. These were done by Igor Batchik, and here's one round, that's eight hours of PMCA and he diluted it again and the second round and the third round and nine rounds and finally 12 rounds and it seems that you can continue out ad infinitum. And the developers say that because you eventually get below Avogadro's number, this must mean that you have created

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de novo lots of new protein; therefore, the sensitivity of the test should be exquisite.

Two problems, at least two problems. One -- this is a side remark. See those little smears down there? You saw some of them in Soto's. That's from the second antibody so you do have to be careful that you have nice, clean reagent because those can be very, very confusing. If that were in a Dot blot you would know by your controls, if that were in Dot blot or ELISA you could read that as positive and if you burn in a gel, that gets even worse.

At any rate, but the most disappointing thing for us was that the increase in sensitivity, here's a standard Western Blot and you've got a positive out to somewhere between ten to the minus three and ten to the minus four dilution and when we did a PMCA, it went out to somewhere between ten to the four and ten to the five. And that's an awful lot of work for a ten-fold increase in sensitivity. Again, we didn't develop the test. We haven't optimized the test. The added brain is a biologically variable

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material.

And there are other problems encountered in developing PMCAs. The most important for our purposes today is that it failed to detect abnormal PrP in some hamster blood samples thought to contain the infectious agent. And I'll show you that in a minute. And then a recent, most troubling report has been has been that a modification of this procedure generated abnormal PrP from normal tissues and that the abnormal PrP-TSE generated de novo was itself infectious.

Now, these claims have not been convincingly confirmed by other authorities. Bob Rohwer has been unable to demonstrate that the generated protein was itself infectious and I understand that Byron Caughey, both very reliable workers, have not. But that's a problem. And then here is a sample from Paula Sigh (phonetic) in Soto's group of the problem with the sensitivity. Remember the tracing from Bob Rohwer's hamsters where halfway through the incubation period the infectivity appeared and it went up and never came down again? They found

detectable, whatever it is, PrP-TSE, which never reached 100 percent, up to about 50 percent of the alloquats tested down to zero at 80 days before rising almost to 100 percent during the clinical illness.

Well, you're not going to be screening blood donors who are clinically ill with Creutzfeldt-Jakob disease but you will be screening blood donors when you're in the end of the incubation period and you know that donors are infectious for at least three years before onset with variant CJD. I can show you those data. So, this is a severe problem.

The problem posed by amplifying abnormal PrP from normal tissues is even worse. The two problems are one, etiological. If it's ubiquitous this abnormal protein would appear to fail one of Koch's postulates, that is, nonubiquity. Now, of course, you're free to junk Koch's postulates if you like but there should be some rules of evidence for what constitutes an infectious agent. But the practical one is that if you increase test sensitivity to overcome these false negatives and it leads to detection of abnormal protein in many samples from uninfected sources, then you've lost specificity and positive predictive value. And this is serious enough that Aguzzi from Zurich put it better than I can, that, "Prions have been generated de novo from purified ieukaryotic PrP with admixtures of polyanions and lipids using PMCA. This discovery is exciting but blows a kiss of death to diagnostic PMCA."

I take some other counsel from two of my esteemed colleagues from the United Kingdom, where the risk has obviously been considerably greater than it is here. Phil Minor commented about UK public health policies and BSE/vCJD, that they have been based on two very important elements, ignorance and fear. We would probably describe those as prudent respect for uncertainty and the precautionary approach but he's more directly spoken than I am.

And then having heard the reports of the spontaneous generation of abnormal PrP from normals, Bob Will in October summarized it as follows: "What is going on? I am completely confused." And, that adequately expresses my response to the new -- I just don't know what to make of it but it could be a real problem for the development of this initially interesting technique.

Just to close, there are surrogate assays that have been reported. 2001, the first several proteins are released into the CSF including 14-3-3. I've go to disclose, I used to get a patent royalty for a couple of years for the precursor of that protein but it's not specific sensitive or feasible for antemortem testing, which might explain why I don't get royalties anymore.

The abnormal protein, not prion protein, or mRNA patterns have been sought in blood, using nonspecific techniques. There was a flurry of interest in erythroid differentiation-related factor, mRNA, of which seemed to be down-regulated in scrapie and some of the other diseases, apparently hasn't panned out as useful for variant CJD and probably not for BSE either because they haven't heard anything more about it. Fourier-transform infra-red spectroscopy does seem to generate abnormal patterns and especially when coupled with neural network learning patterns for recognizing abnormal patterns better it may offer something that it hasn't yet.

Invalidating any of these tests, it will be important to have biological reference materials. There are two of them I'm aware of in development. The WHO has a collection at NIBSC under Phil Minor's supervision. That collection has been described in a couple of places. I have listed here the European Union has also developed a NeuroPrion Blood Diagnostics Project.

I know they have collection of sheep blood, infected sheep blood and I'm sure that since they work with monkeys anyhow they'll probably -- although I don't know that for a fact -- would probably be aimed at getting infected and controlled monkey bloods; getting human bloods, while important, have been to date almost impossible to get in volumes adequate to serve as reference material. We don't have a U.S. reference material but working together with Larrisa

Cervenakova in Roger Dodd's group and Pedro Piccardo in my group we have done infectivity titrations on three of the World Health Organization references and the Swiss BSE reference material.

And this is what I meant to show you, that we had to do the variant CJD titration in FEB-nontransgenic mice because the PrP-humanized mice are not susceptible to variant CJD. So you have to be careful in predicting from a sequence that you put into a mouse what its susceptibility is going to have to be. It does have to be validated in a traditional way.

And I'll close. I can't add anything to the discussion this morning by Drs. Dodd and Roberts about whether a validated TSE tissue blood donor screening test would be indicated in practice. For tissues it's feasible. Now it would require doing autopsies and validating the test with a very small market. For blood, based on what Granger Morgan calls -- he's an engineer who does risk assessment -- calls utility-based rules, you'd go through the kind of risk-benefit analysis, looking at the risk-benefit, maximizing the benefit and accepting remote risk only if you had to achieve a substantial net benefit.

And, by the way, a false positive TSE screening test without a valid confirmatory test to our mind would plausibly constitute a substantial risk to the donors. I mean, it would be very difficult to tell somebody you got this stuff in your blood, we're not going to take you as a donor anymore but we don't know whether you're going to come down with a fatal disease, or, it's nothing. It would be very difficult to deal with a situation like that.

To my mind, if the number of BSE cases or the number of transfusion cases continues to go up and they reach a level where public perception causes a considerable amount of concern, and an adequate test becomes available, which is not for blood donor screening, then it's likely we would shift to what Granger Morgan calls technology-based decision rules, which is to use the best technology available. If you have a test and it works and the disease it interdicts is serious, it is very hard to tell a population that

we're not going to use it but if the cases in the UK continue to remain low and the BSE epidemic continues to devolve, then we may well accept the continued risk even if a reasonably effective test is developed. I'll stop there.

DR. BRACEY: Thank you for that thorough review. I think it clearly answers the current-status testing. We need to take a break now in the interest of time and reconvene at twenty after -- well, we can try quarter after.

(There was a break in the proceedings.)

DR. BRACEY: Okay. Our next speaker is Dr. Harvey Alter. He served as Chief of the Infectious Disease Section and is Associate Director of Research in the Department of Transfusion Medicine. Dr. Harvey Alter is old enough so that he is the coinvestigator on the original discovery of the Australian antigen test, really done seminal work in terms of helping to chronicle what used to be known as nonA, nonB hepatitis is now known as HCD. He's received numerous awards including the Lascar Award for his extensive work in

the field and he will present a reductionist's view of the pathogen reduction. Dr. Alter?

DR. ALTER: How are you doing? First, Jerry, I want to thank you for this wonderful time slot. While waiting my prions have undergone a confirmational change. In any event, there is the obligatory disclosures to make to begin with. And I have to discuss that I both work for and am a victim of DHHS, which is "diffuse hereditary hypertrophy of the scalp."

In the wake of the HIV tragedy the FDA and the U.S. blood establishment have endorsed the precautionary principle, and I think it's worth just reading this again because it's key to our decision. It says for situations of scientific uncertainty the possibility of risk should be taken into account in the absence of proof to the contrary. And a corollary to that is the precautionary principle asserts that measures need to be taken to face potential serious risks. My own corollary is that pathogen reduction is really the ultimate precautionary principle by

eradicating almost all potential for infectious disease transmission even before that risk has been conclusively established and possibly even before it has been recognized.

So, I think this is a new paradigm in transfusion safety that may initially add costs but ultimately I think will not only provide maximum safety but will actually turn out to be cost neutral and probably cost saving, as I will try to define later.

Now, this variation of our prospective studies shows the decline of posttransfusion hepatitis, as was shown earlier, today from about 30 percent in the 1970's to near zero by 1997. And that's been viewed as one of the major accomplishments of blood transfusion medicine. But in the context of today's talk, I'm chagrined to say that it's really one of the major examples of a failure of transfusion medicine.

Because there was no preemptive viral reduction strategy in place, because decades passed before agents were recognized, before the extent of the hepatitis risk was really defined, before the agents

were discovered, before proper testing strategies were implemented, a huge number of cases, I've calculated that hundreds of thousands of cases of posttransfusion hepatitis occurred over the decades from 1970 to 1990, before we could do anything about it or before we chose to do anything about it. And that's, so that's, that's the one point.

Now, historically, there has been a very long interval between the first recognition of the disease, that a disease be transfused and transmitted and actual implementation of the first screening test. Now, for hepatitis B that interval was 1940 when it was recognized in World War II, for the first Australian, antigen test in 1970, a thirty year interval. For nonA, nonB HCV that interval was 15 years. For HIV the better value reduced to three years, for the first recognition of transfusion-transmitted cases and for West Nile virus we did increasingly well and we reduced to under one year.

However, if we go back, we actually have warnings that West Nile virus was transmitted by

transfusion in 1999. So, it really can be viewed as possibly four years. And then Chagas disease, which was recommended by the Blood Products Advisory Committee in 2002 as a test we should be doing but it wasn't till 2007 that the first test was implemented. So, the inherent problem is that this kind of reactive strategy to pathogen risk is a fundamental and inevitable delay between the recognition of risk and the prevention of risk and thus infections are just destined to occur before we can adequately react.

So, West Nile virus is a good example of this. As the West Nile virus epidemic began to spread rapidly across the country in 2002 we had nothing in place. We had very little we could do to prevent transfusion-transmission. Once testing was developed in 2003, we did very well. But there were 23 cases, documented cases, and probably many more in 2002, and according to CDC estimates of 140 infections for each clinical case, there were probably actually 3200 or more infections of West Nile virus from transfusion in the year 2002. As you can see, it declined markedly

after our testing but overall there were 32 cases or 4480 infections from blood transfusion.

So, it's a lot. It's not like hepatitis but it's still a lot of cases. None of these cases, not a single one of these would have occurred if we'd had had a preemptive strategy in place. And proof of that is that not a single case occurred from solvent-detergent treated plasma. This inactivation works. It would work for this agent. It would work for Dengue. Are we going to repeat this for Dengue now as David Leiby implied? Dengue has all the characteristics of West Nile -- the spreading mosquito is already here -- the only difference is it doesn't have the bird host which facilitates its spread.

So, in the final analysis, and you can see some pictures I have from Africa, what you see here, even the King Buffalo has an onboard pathogens surveillance system. But, the bottom line is that any agent that even transiently traverses the circulation of man during an asymptomatic phase of infection is a threat to be transfusion-transmitted and the likelihood

of that transmission is highly dependent on the duration of viremia -- or whatever the agent is -- and the level of concern is dependent upon the severity of the ensuing disease. So we now as we have already heard today we have whole panoply of unscreened threats facing us.

Now, fortunately, as chikungunya becomes a problem, it will now be much easier to handle because my lab has determined the crystal structure of the chikungunya virus.

(Laughter)

DR. ALTER: Now, this vast array of potential infectious agents requires continuous surveillance and then a clinical assessment of the magnitude of each identified potential risk and then, where possible, testing or other strategies to limit that risk. So, this is an agent-by-agent reactive process that is inefficient, insensitive, often controversial in its decisions and inevitably applied only after disease has occurred. A more encompassing, efficient and intuitively appealing option is

preemptive pathogen reduction. And I'm really just here as setup man for tomorrow's program, so, but I will express my opinion.

So, almost all the aforementioned agents and many others can be reduced to nonpathogenic levels by these nucleic acid intercolating agents such as psoralens and Riboflavin in the presence of UGI. Now, shown here are the log reductions for psoralen EVA and much the same could be shown for Riboflavin. These are very significant reductions, and may be even higher. We just don't have the test system to really know how the about how high the reduction can be. So that's encouraging.

And, pathogen reduction has many potential advantages. First, it effectively inactivates most clinically relevant viruses, whether they're RNA or DNA, single-stranded or double-stranded, enveloped or nonenveloped, intracellular or extracellular. It's really incredible but it does that. It inactivates all the clinically relevant gram-positive and gram-negative bacteria that have been tested so far. It inactivates

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Spirochetes for catching (phonetic) protozoa of known transfusion relevance. It prevents transfusion associated with graft-versus-host disease by killing lymphocytes. And it offers the probable preventative, protection against pathogens that may be lethal, it may be another AIDS agent some day -- that will inevitably emerge in the future.

So, in this regard it's really like a magic bullet. It has these incredible advantages. But there are impediments to pathogen reduction that have limited its use. First of all, there's been shown to be some decrease in yield in the platelet trials perhaps 10 to 20 percent, but the clinical effectiveness was marginal and virtually any technique including sense irrigation will reduce yield by perhaps 10 percent.

The second point, a small one, is that there has been insufficient kill of some high-titer agents, such as HAV and Parvo B-19 but these agents, the recipient population has antibody at very high levels and the reported cases of either of these agents are very, very few.

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Toxicity has been a big issue because indeed no toxicity is known for Riboflavin. It's a natural -- product, and the risk from the psoralens is really theoretical at the low residual doses that would actually be transfused. There's a built-in, very wide safety margin. There is some concern in pediatric cases but even here the margin should be wide. So, the main deficit or detriment I think has been that one, there is no process as yet that's proven to work for red blood cells and therefore no single process that could be used for all blood products. And I'll get back to that argument in a moment.

And, then again there's great fear of projected high cost but there are offsets to the cost. If we could develop the multicomponent pathogen reduction system which would include red cells, then we would reap I think some cost benefits.

And, first of all, we can eliminate some of our current assays. I believe that testing for syphilis, anti-hepatitis B core, which loses about 1 percent of our donor population, Chagas disease, which

we just started but I think we really need it and I think get rid of West Nile virus and possibly others. We would preempt the need for future testing, things that are probably coming down the pike, like babesia, Dengue, malaria, HHV-8. We could eliminate bacterial testing. That would be a major cost-saver. We could eliminate radiation, prevent graft-versus-host disease, another cost saving, and, a very big item is it will allow us -- and we're sort of on a trend now moving from minipool testing to individual donor testing but this would allow us to continue minipool testing and still feel safe. And, we could reduce donor exclusions based on geography. And we have heard today how many donors we lose because of the malaria exclusions.

So, cumulatively these measures would be really a major savings and relieve a lot of headaches. But perhaps the key and immediate addition really is not the efficacy. I'm going to kind of get on a -- there's a line I'm going to use so you don't fall asleep -- I'm going to get up on a soap box here and say that I think the immediate key issue is not really

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the efficacy of pathogen reduction because the evidence is substantial, and not even the safety, where the toxicity remains theoretical but rather whether we should introduce pathogen reduction for platelets in single donor plasma before a system is in place to inactivate red cells.

This is a strategy that has been adopted in many countries in Europe. It's a difficult conundrum. I'm not sure I know the answer. Opinion is very sharply divided on this. However, it's known that many patients receive repeat, often daily platelet effusions that only intermittently are accompanied by red cell infusions and also that many centers pool platelets, vastly increasing the exposure risk. It's also clear that if we wait for the complete system another five to ten years is going to go by before that's in place. And, during that time, platelets and fresh frozen plasma are going to continue to transmit infectious diseases, at a low rate but nonetheless they will transmit them.

Should it turn out that there's a new agent that comes along that is more serious, then further transfusion-transmitted tragedy will ensue. I believe that the precautionary principle and the moral imperative dictate that we implement what we have even if it's less than perfect. Admittedly there's the other side of the coin and that platelet single donor plasma activation in the absence of red cell inactivation will not bring us the cost savings that the complete system will and that red cells will continue to transmit diseases. It's also clear that pathogens are only a part of the risk equation, and now not even the largest part, as we saw today; however, I counter that correcting human error or trying to prevent human error and introducing methods for TRALI in pathogen reduction are not mutually exclusively and they all should be pursued with equal vigor.

Solvent-detergent treatment of commercial plasma and its derivatives has established the principle that pathogen reduction of even a single blood clot is enormously valuable and has simultaneously established the principle of preemptive pathogen reduction. Universal solvent-detergent treatment has rendered the formula, most risky of blood transfusion products, plasma and plasma derivatives, will now be the safest. As blood transfusionists scramble to find a way to stop West Nile virus from whole blood and platelets, how reassured the plasma industry must have been to know they already had this agent preemptively covered. Those same measures would protect against Dengue in plasma or any lipid-encapsulated agent that threatens the blood supply.

Had we had solvent-detergent treatment in place in the early 1980's, the vast majority of cases of HIV and HCV that afflicted the hemophiliac population would not have occurred. And I say this not to cast retrospective blame but to take a lesson from history and to illustrate the value of having a protective mechanism in place before the next agent strikes us.

At present we have two technologies, psoralen and Riboflavin, that would give the same level of safety of platelets and fresh frozen plasma that we currently have in commercial plasma derivatives. Can we risk the possibility that a new lethal agent will enter the blood supply and replay the HIV tragedy? Can we face future generations and say that we did all we could at the time? I believe the time has come to act. The evidence for safety and efficacy of pathogen reduction in platelet and plasma, both here and in Europe is sufficient, if not overwhelming and any reasonable interpretation of the precautionary principle would say that this a procedure that should be implemented.

However, whether you agree with that or don't agree with that, that is not my main issue. My main issue is that we have to establish a mindset that says that pathogen reduction of all blood products is a worthy and achievable goal. And we need to invest ourselves emotionally, intellectually, and financially to make this happen. The blood bank establishment, NIH, FDA and industry have to make this concept a priority, something they haven't done as yet, and then work in concert to devote substantial resources and energy to achieve this goal just as they did for viral nucleic acid testing. Only then will this happen.

I was in a packed ballroom in a hotel, I think in Silver Spring, around 1996, when David Kessler urged blood banks to develop NAT testing for routine donor screening. Everybody said "yaw-yaw-yaw." It was huge, huge skepticism over that. But because of his position of authority it really drove the system. It generated government-industry collaboration and resulted in a remarkably rapid development of NAT testing that had been just of immeasurable benefit to blood safety.

Now, I'm no David Kessler and I have no position of authority, but I admonish you and I encourage you to say that this is the right thing to do. We don't have David Kessler here today but I think he might agree that this is the right thing to do, whatever right is, and that we have to find a way to do it. We have to bite the bullet, and, fortunately in this case, it's a magic bullet. So, thank you.

DR. BRACEY: Thank you. Any questions or comments from the Committee for Dr. Alter's presentation, which I think was quite clear? Ms. Finley?

MS. FINLEY: Thank you very much, Dr. Alter. I hope that the Committee will have the benefit of seeing your slides. We don't have them already.

DR. ALTER: Yeah, they're going around the room.

MS. FINLEY: Great. Thanks. I did want to ask you to, first of all, if it's not an inappropriate question to ask if in front of our FDA colleagues. Where are we with review of psoralen and, et cetera?

DR. ALTER: Well, yeah. I mean, I can't answer that. There are clinical trials in process, that there have been clinical trials that have been done that have shown that it was sufficient for European countries, many of them, to introduce routine platelet pathogen reduction. The data were not sufficient to the FDA but new trials were underway.

MS. FINLEY: Whose product is that?

DR. ALTER: That is, Cerus is psoralen, and Navigant is Riboflavin.

MS. FINLEY: Okay. Thanks. Just getting to the point that you made about incremental improvement in the safety of the blood supply, I'm sure you are aware that the Department responded to the Institute of Medicine report in 1995 regarding the mistakes that were made in transmission through the blood supply of HIV and HCV. Principles for incremental improvement and for behavior of physicians, the government, the industry, blood testing facilities, et cetera, were very, very clear about how we respond to infectious agents.

I was wondering if you felt comfortable responding to the role of incremental testing improvements in view of the commitment the Department has made in sworn testimony to the Congress, which, as far as I can tell, it's still where we stand in this country regarding blood safety issues.

DR. ALTER: Well, I'm glad you asked that because I don't want to denigrate what we've done. I

mean, we started late.

MS. FINLEY: Yes.

DR. ALTER: And I think we've done our mea culpas about the late start but once we started, once HIV came along, we have been incredibly vigorous in the precautionary principle, in truth, and in doing anything we could to prevent disease transmission and it's been highly, highly effective. But, it's just this inherent problem of reacting to something and just by definition if you are reacting it has to have already occurred.

And so by the time -- and some tests are easier to develop than others so we got the West Nile testing very fast. We already had a platform in place but if it was a totally new agent, might take longer. So, we've done a great job but now we're at this impasse where the number of agents, mosquitos are attacking us from every side, ticks, and everything. There's just a lot of agents out there. They're not as devastating as HIV but we don't want to transmit them. I don't think you want to transmit them. And by going

down this pathway -- which if it can be done, and I don't even know if can it be done. I don't know if we'll have a red cell system actually work in practice. I just don't know that. I'm just saying we've got to try to get there. And, but if we got there, it would be wonderful. We would already, we would feel really safe. We would prevent everything except prions and we could eliminate a lot of things.

I think I listed some of the things but there's probably some other things we could eliminate and if we just eliminate questions, we would increase our blood supply by 2 percent just by eliminating the malaria questions and any travel restriction questions and by not testing for anti-HVC. That's 2 percent right there. The benefits are enormous.

DR. BRACEY: Thank you, Dr. Alter, for the judicious use of time.

DR. ALTER: That was just my first slide.

DR. BRACEY: No, no. I think now is a good time to move onto our next talk. It will address some of the questions related to the use of these agents.

This talk given John Chapman, vice president of research and development for ThermoGenesis. The topic of the talk is toxicology related issues of pathogen reduction. Dr. Chapman has done extensive work in this field. We're very fortunate to have him today to share his information. Thank you.

DR. CHAPMAN: Well, thank you very much. It's a pleasure to be here to have this opportunity to address the Committee. I, like Dr. Wright, am from Texas and so hence you already introduced into the record that it's a great state, I'll forego my usual overview of the Texas history.

DR. BRACEY: A great state with mosquitos at risk.

DR. CHAPMAN: So, my subject matter of expertise is toxicology. And I was actively involved in the development of pathogen inactivation technologies from 1988 to 2004. I did this for particularly red cell technology, Inactine, the latter part. Since that time I've disengaged from that work so I don't have anything to disclose in terms of any

relationships with anyone. But, I am very interested in the field of pathogen inactivation and I appreciate that Jerry has called me and invited me to come and talk about toxicology and I hope that my comments will be useful to the Committee.

This first slide just shows that you can divide the national blood supply into two categories, blood components and plasma and, as Harvey mentioned, pathogen inactivation has already been introduced into this and the performance and safety record that is really impressive in terms of how well the introduction of pathogen reduction has achieved in improving the safety. On blood components you can see the scope of the problem. There's 14 million units collected from 8 million donors approximately and those end up being transfused into 4 million recipients. So, you, there are a large number of exposures going on here and so have to see how we can maximize that safety as well.

And one thing that I want to talk a little bit about, apart from the toxicology issue, is it seems like there's a lot of focus on the first case of a

small population of infected people transmitting virus to the large population at risk. But where I also have a lot of concern, especially when I was working, is about the other, going the other direction, where you have populations that have CMV and EBV, which are, you know, 70 percent of the population may be seropositive but 30 percent of the people going into a hospital are seronegative for CMV.

And, so, that's a lot of people. That's nearly 1 million people are seronegative going in. And, the data is not very clear about what is the frequency of that transmission, maybe 1 percent, but if it is 1 percent that's 10,000 people infected with CMV. And, it has to be very optimistic in my view to think that there's no harm being done by that. What is the harm? I don't know. When I was doing this work, I looked for that data and it's really absent. So, I think we also have to keep in view not only thinking about this kind of case but also this case because I think those could be important as well.

Now talking about pathogen reduction

technology, there is a general theme that emerged over the last 15 years of developing these, and, you take a blood product, the first thing is to deliver the compound to the blood, the reaction occurs, it can either be a spontaneous reaction or more commonly known now to be photoactivation, triggering the chemical reaction and then for most of the processes there's a compound removal step to further enhance the safety aspect. You then have a pathogen-released product which can be stored or transfused.

During the 15-year period that these technologies were developed one thing that came out was that you need to target nucleic acids because that provides a biochemical basis for selected toxicity and if you don't have that you really couldn't be successful. And we looked at many different ways to inactivate virus, such as oxidation, many different chemistries and none of those worked until we started targeting nucleic acids. And it's really the absence of these pure specificities for nucleic acids that gets technologies into trouble, actually.

So these are some of the examples of the companies that are actively developing this. Inactive 10-110, you don't hear about that anymore. That's something that I used to work on. And also S303 is not actively going on in the trials now as I understand. Both are the two red cell technologies but still the Methylene Blue is not being used in the United States, there's a lot of intellectual property issue with that but the psoralen technology and Riboflavin is moving forward.

One thing I want to emphasize from a toxicology perspective is it's important that people understand that the FDA is very, very important in how these technologies are developed. So, you go through the -- use of process developments, nonclinical study but once you get to that point of nonclinical studies, the companies are engaged with FDA and the studies that are done, the experiments, it's a continual exchange between the FDA.

So that relationship is very important. It's really vital to the development of technology and

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also it has a lot to do with the overall safety assessment. Because it's not like we do all these studies, phase one, two, three and then do all the toxicology studies at the end of the game and say, okay, now let's review that. We have continuing conversations with regulatory agencies so it's continually monitored and I think that provides a lot of assurance that the products will be done in a safe and effective manner.

This slide is one from Dr. Vostal. And I think it's a really important slide for the Committee because it's just like Dr. Alter was saying, until there's a clear acceptance that there's a benefit for this technology -- which I don't think there is yet -- then the amount of risk that you can put into the blood system is determined by that level of benefits. So, if the perception is that there's very little or no benefit to the pathogen activation technology, then you can justify putting almost no risk into that and then the issue of theoretical risk becomes even unacceptable.

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So, I think if it was clearly stated that we need this technology, then we would have more of a platform to really look at the risk. And, of course, the whole purpose of the toxicology part of the program is to assure that we're doing risk reduction, not risk substitution. We don't want to introduce chemicals into the blood supply and introduce a new type of risk. We actually want to do a risk reduction.

So, how do we go about knowing that, as a toxicologist, how do we apply that discipline to the assessment of risk? Well, really there's two basic categories of work. One is exposure assessment; that's emphasizing that dose is critical. The outcome will be largely determined by the exposure, how frequently does it occur, and what is the magnitude, and then understanding what the is the hazard of the chemical, what is the nature of the substance, what kind of infection is produced and then collectively that gives you the information to do a risk assessment.

And, just like for drug development, there are standard batteries of test information that are

required to characterize the toxicity of a compound. And so a list here is provided and these have all been done and published in many phases for the psoralen technology and then also for some others. But these are the standard work that's done. It's very expensive work but it's necessary and it's routinely done.

Because these agents target nucleic acid, there's really a strong focus on what is the genotoxicity. And, so, you have a battery of assays or not just one genotoxicity test that you do and say it's a pass or fail. You have in vitro mutagenicity assays; you have in vivo mutagenicity assays. In vivo are particularly important because they take into account the biological factors of absorption, distribution, metabolism and excretion that can affect what the actual risk is for an adverse health effect. These are the assays that are there.

Then finally and very importantly is the carcinogenicity bioassay. Now, with the transgenic mice model being available, the P53 mouse model you have a shorter time to tumor, reduced number of

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animals, still get the benefit of the whole animal dosimetry and all those are being performed.

We have two types of test articles that we use for toxicology characterization. One is the, what I call product safety studies. In this case you take the test article for the study with the, in the case of the psoralen product would be the psoralen-treated platelets and so what you do there is treat the platelets and then you actually use both as a test article in an animal and you just give as much as you can. So the exposure maximum is volume constraint.

The other type of study are more of a classical risk assessment for the active ingredient, is the test article, so, for example, S-59 would be a test article and there you can just keep going and you will produce toxicity. You can find out what is a maximum tolerated dose. And so both of these kinds of studies are very important and are being done for these compounds.

So, before I get into some of the details of the data, I'll just give you some generalizations

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about what are the kinds of findings that we're seeing for those compounds that have made it into clinical or phase redevelopment. And, the active agent for these compounds can be demonstrated to have toxicity but they're consistent with most drugs, in the range of 1 to 100 milligrams per kilogram, be some evidence of a biological effect on the recipient. However, the exposure that actually occurs is much lower than that and routinely we can demonstrate greater than a thousand-fold safety margins.

And this thousand is important because for general toxicity endpoints you try to have a ten-fold safety factor for extrapolating data from animals to man because animals are not a perfect model for humans. You have another ten-fold safety factor built in because not all humans are similar versus susceptibility for chemical insult, and then finally what is another ten-fold factor and that's just for variants in toxicology endpoints. The science of toxicology is not perfect so it blunted (phonetic) another ten-fold safety factor and so when you go ten times ten times ten that gives you a thousand-fold. And so you really have a feeling of confidence in the safety you can achieve through a thousand-fold safety factor.

I think one thing that is very important is that people understand, who are evaluating these technologies, is that the residual level of the active ingredient in a fully processed pathogen blood component is below the detection limit of toxicity assays including genotoxicity. That means that if you take a unit that's not treated and a unit that is treated and you ran any toxicology test that you could conceive of, I know of no test that can differentiate a treated unit from an untreated unit in regard to a toxicology endpoint. So, that's the efficiency of removal. So, as Dr. Alter was saying, there remains a theoretical risk but it's not a measurable risk in terms of actually being able to identify a pathogen inactivated unit based upon a toxicity endpoint.

Another point I want to talk about is the potential for long-term toxicity. The active agents that are used are water soluble and so they would be excreted rapidly without accumulation in the body. If they were highly lipophilic, then you would be concerned about potential for buildup. One of the challenges for risk assessment, however, is there are diverse reaction products of the active agents in the blood component so when you add the pathogen inactivating agent to the blood, there are biochemical reactions, some of which are covalent, and these create species.

And there can be many of these species. So, it's difficult to really build up safety margins on all of these different species that are created; however, what we do know is that the reaction products are generally less biologically reactive than a parent compound, so I don't know of any phase where there's a derivation of the parent compound into a more active or toxic form. So, if you can demonstrate safety with the active form, I think you have a very good safety margin for side products. But if it is a limitation of a technology, it's much easier to characterize a very high safety margin for the active ingredient and the reaction parts are more difficult to do.

Now, this is a summary of findings for Amotosalen. I still want to call it S59. I guess I'm an old-school guy but I wish we would have chosen a little easier name than Amotosalen. But the point of this is saying to demonstrate first all these types of toxicology studies that would be done for a drug are being done for a compound. So you see acute toxicity, repeated dose, subchronic, reproductive toxicity, phototoxicity, and they identify what is the maximum no-effect dose.

Okay. So what dose is required to get at to a point where you can get to a point where you can see no measurable effect in an animal and how does that relate to the clinical exposure? And you can see you get can very good safety margins for all of these endpoints. And that's quite an important finding.

And, I really want to bring attention to the Committee about this publication because it's really a hallmark for the advancement of the toxicology of pathogen reduction. It's a paper studying the genotoxicity assessment of S59 and it's published in a highly-respected research journal, Mutation Research, very prestigious journal, and it is, for those who are really, truly interested in what is the genotoxicity of S59, the data is presented very clearly, it's comprehensive, it's well-thought out, it's well-presented, and really I think is the standard to which all toxicology work should be held to. And I was very appreciative to see that this kind of detail is getting out into the public literature because, you know, sometimes it's difficult for this information to be available.

But the conclusions of this paper were that the genotoxicity studies discussed here support the conclusion that the technique does not cause a relevant risk with regard to mutagenicity and carcinogenicity. That's not to say that there's an absence of mutagenicity because they show in vitro, you can see evidence of mutagenicity; however, they're putting it into the context of the in vivo setting and the exposure levels, and that's what's resulting in this conclusion.

The safety margins are extremely impressive, the no-effect level. We have more than a 40,000-fold safety factor there, and also, they report, in the mouse bioassay for carcinogenicity that it was negative. So, key findings for the assessment.

I want to talk a little bit about work that I was involved in with the Inactine PEN110. This was a red cell inactivation compound. It's an alcholating agent. And I think it will give you some perspective for how to look the a carcinogenicity data.

So, the way this study was done is to look at giving different doses of PEN110 in the animals, 0.45, 2.25, or 4.5 and the test article is the active ingredient. Route of exposure was intravenous. They gave the compound three times per week. There's 28 animals per sex per group. So, this level of exposure of 0.45 milligrams per kilograms was equivalent to the amount of PEN110 that would be present in 18,000 units of red cells. And, so, cumulatively over the 26-week

period these animals received an equivalent of 1.4 million use of red cell PEN110 compound, just dose escalation.

Now, the reason why this number is so high is because of the extent of removal. We had one milligram per milliliter as the concentration during the inactivation step but we needed a four-log reduction of the compound for removal so that there's only 50 nanograms per milliliter. So that's why these numbers are so incredibly high.

If we look at the results, we can see that we were able to achieve a positive endpoint in the bioassay at the highest dose. There's a clear increase in the incidence of lymphomas and sarcomas and that effect dropped off very quickly. So only at the highest dose did we see an effect but we did see a positive. So one headline could read, "Inactivity is Carcinogenic," but it has to take into account that to achieve that both animals over the duration of the experiment received the equivalent of 14 million red cell units. So that's a pretty impressive

accomplishment.

Now, so, but you can analyze this data and there are very disciplined ways of looking at this type of bioassay data in terms of projecting what does that mean in terms of likelihood of increased cancer in the population. And if you did that, the projected increase in cancer rate would be 0.105 additional cases per year. And, of course, that's a very small, a trivially small number compared to the 1 million spontaneous deaths per year. But the point of showing this PEN110 data -- because it's not in consideration and I'll talk about why in a moment -- but this compound is more toxic in its genotoxin spectrum than the psoralen technology is. So, however you feel about this data, you should think about the psoralen data being even safer than this.

Now, another key aspect of the safety was the clinical trials. And, we had a case where for both S303 and for Inactine, PEN110, that we saw, an immunogenic response was observed to the Inactine-treated cells. And so we first saw this in

sickle-cell patients and then we saw it in surgery patients as well, not very commonly, just 1 out of 50 patients, but, what the manifestation was, was that the patient became DAT-positive during that trial. And those trials were stopped voluntarily by Vitex and no harm was done to the patient.

And I think this is, the key point here is that the appropriate clinical trials are being done to ensure the safety and that if there is a problem studies are stopped. This was, stopping this trial was the loss of $100 million in investment for Inactine. So, I would just say for Harvey's point, I don't know if in five years there's going to be red cell technology or not if you don't do the psoralen technology because who is going to invest in after you drop $100 million, and get nothing out of it, what's your motivation to go in if the agencies are not willing to move forward with the existing technology? I don't think the red cell technology is going to come if you don't do the psoralen project just by pure business reasons.

Now, I want to talk about something that looks like a little bit off the topic but I think is very relevant and that's the ethylene oxide perspective. Ethylene oxide is like the blood sterilant is used to inactivate microbes, has a removal step, there's some residual ETO maintenance device and that results in in vivo exposure.

And, ETO, what happens is that this residual ETO can reach into the fluid path resulting in human exposure just from this trace amount. ETO is a very hazardous substance. It's a highly reactive alcholating agent. It's mutagenic in vivo. It's carcinogenic in animals. It's only one of less than 30 compounds that are recognized to be a human carcinogen. It's fetotoxic and teratogenic. It's a reproductive toxicant and it's a fetogenic compound as well. So, if you stack up how does ETO compared to the other pathogen activating agents, you can clearly see that it's quite a stronger hazardous material.

Now, but it's allowed to be in these products and it's regulated and there are regulated

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limits of ETO human exposure. So, and they divide the exposure category into a limited exposure, prolonged exposure or permanent contact and they define what does that mean by the duration of exposure and then they looked at the average permissible daily dose, 20 milligrams, 2 milligrams per day, 0.1. For apheresis devices and hemodialyzers you can have 20 milligrams of extractable ETO per set and for blood separators and oxygenators you can have 60 milligrams extractable ETO per set.

FDA is recently looking at giving guidance to the industry for core blood processing and so the intention is to allow for core blood processing but they can allow up to 5 milligrams of ETO to be core blood. So, this is looking at how much ETO can you recover when you flush the system with saline.

Now, if we compare the ETO exposure limits that are regulated and permitted to those that are anticipated with the pathogen activation agents, you can see that the margin is tremendously different. So, for apheresis if you have 20 milligrams per device,

what we would say for psoralen, you expect to have 0.05 milligrams. So that's, for the 60 milligrams it's a factor of 1,000 more ETO allowed than what we would have with Amotosalen.

So, if you look at the exposure assessment, we have much less exposure of the pathogen reduction agents than with ETO. If you look at the hazard system, ETO is clearly a more hazardous substance, then you would make a reasonable conclusion, I think, which is that you have less risk associated with the pathogen reduction agent than with ETO and yet that's the dilemma. That's currently, so if you're afraid to go out on a limb, saying we're afraid we're going to cause harm because of this theoretical risk, you are at a much stronger position than you are today with ETO and that's widely used and widely accepted in blood products.

Okay. My summary slide shows that whenever you introduce pathogen inactivation, there is a potential to produce hazards and we utilize toxicology testing to identify those hazards, characterize them

and to estimate risk. I feel strongly that the appropriate toxicology testing is being done and that this is being done in partnership with the FDA. We have worked with the agency to make sure that we're doing the proper, appropriate studies and communicating those. It's very important that we have open communication of all toxicology findings and I think that's improvement and I congratulate Cerus on publishing their results because I think that's a very positive step for the field.

It is true that, however, that only the FDA and the companies developing the technology have complete access to the data so my perspective that I'm giving, I don't have access to all that data so we have to confidence in the FDA to appropriately evaluate the data because not all of it is public and nor should it be.

Finally, I think the final point I was trying to make with ETO is that we need perspective, and that perspective should look at what risks are we currently allowing to go forward, and I think the

benefit of the pathogen activation technology is such that I am an advocate for it moving forward and I hope it proceeds with success. Thank you.

DR. BRACEY: Thank you, Dr. Chapman, for sharing that data with us. Questions or comments from the Committee? I think it was clear. Ah, one question. Dr. Epstein?

DR. EPSTEIN: Well, only to point out that we review the toxicological data as preclinical information, which is part of the threshold for allowing clinical studies, so, to a certain extent FDA has already reviewed and accepted the reasonable safety of these agents at their residual levels because we allowed the clinical trials. So, I just think it's important for the Committee to understand that this isn't really where the field is hung up.

DR. BRACEY: Thank you. Dr. Benjamin?

DR. BENJAMIN: Well, I want to make a comment that in public perception, it may not be the FDA's criteria , but when you talk about pathogen inactivation people will say what about these drugs

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you're putting in them, so, that's a different issue.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: Just briefly there has been a lot of public discussion, you know, we're brought issues to advisory committees, there have been workshops, conferences and the like, and the question of residual toxicity of the inactivating agents is always addressed. So, you know, because it's part of a dialogue I guess it, you know, captures attention but again speaking strictly from the FDA's point of view we have accepted the adequacy of the preclinical data. We have allowed clinical trials.

DR. BRACEY: Thank you. We will now move into the public comment section. We have called Dr. Cumming, who is President of Talisman Limited and he will make a comment on quality donor system. Dr. Cumming?

DR. CUMMING: Thank you. My apologies to begin with. I forgot to note that I'm the owner of the Talisman, and it should be noted on the screen. The purpose of this presentation is to acquaint the

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Committee with the safety benefits to be gained by employing audio-visual touch-screen computer-assisted self-interviewing system as opposed to any other methods that are being used in blood centers. One of the things that the computer does is gives you some of the advantages, it standardizes. For those of you unaware 75 percent of all FDA errors surround the donor interview and the donor processing of the donors, which is why we're concentrating on that. We're getting a more classical perspective on quality and areas of safety, get rid of the errors, essentially.

The results, blood industry, good enough to support us -- and while there's others in the arena, in the field, no one else collects any data and no one else is near as far as along we are in terms of we're doing, our technology is being used in more than half a million units of foundations a year right now.

The ultimate way of introductory remark, we had several authors from on here, in addition to me number of people in the field, good enough to dig out the data do the hard work including Lou Katz, who I

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consulted for years in the development of this technology. He's from this the Midwest. As I said, there are several systems in place right now besides ours. As far as we know one of the major differences is no one else is doing mobile systems other than us, that is, we do the systems that are out on the bloodmobile as well as six sites. Something in the range of 75 percent of all blood is done in mobiles so if you can't do it on a mobile, it's not going to be of benefit to donors.

What else? These are the results of four or five years of research which MXLVI has good enough to support and we thank them very much because if MXLVI would not have supported us in this technology clearly we would not be in the market right now. And, as you will see, I believe, it has substantial safety benefits, too. We are also focusing on this presentation just on the safety benefits, not on a lot of the other ones such as donor satisfaction. Donors prefer the technology to face-to-face interviews, for example, by factors as large as five to one, more or

less.

This is what happens when you totally, in one center, totally standardize the -- there it is. There we go. Okay. You can see when we implemented the technology, which was implemented in 2003, and you can see the rate of high-risk deferrals increasing thereafter, and we were going back and look at it now and see if it's still going up. You can see the repeat donors are much lower than the first-time donors, which is normally the case; the combination is much higher. This is when you put a basically a machine in place as opposed to people facing other people with embarrassing questions.

This is high-risk donor behavior, looking two side, on a before-and-after basis and as you can see, this is pre and post QDS. QDS is our trade name in the field of our system. It's a lot easier than saying AVT-CASI or anything else, and it's all we have. You have the same technology but you change some of the pictures, the audio, you get some deviations. This is what, the data that's come out of that technology. As you can see here, what we have is the "before," which is the, for high-risk deferrals and first-time donors, pre-and-post QDS. The "before," it's much less in those little white-blue areas on a rate per thousand basis than it is post. And there's more variations in pre-numbers in terms of the size, whereas the post numbers, you go up to a much more consistent kind of number, which is what you'd expect from standardization.

In another area staff errors and omissions, which is a big area for reports to FDA, it has the other effect. You are eliminating errors again and you are reducing the number, in this case per thousand basis up to from over three, four or five, down to less than two in both cases.

This is looking at the initial test positives, again, first-time donors, which is where all the high-risk behavior is, at any rate, and you can see there that it goes down. The bottom line there is there is 27 percent reduction in the rate per hundred thousand for initial test positives on screen. This is

27 percent reduction, and you get that whether you are looking at number of units, which is much less clear than it is when you get the rates per thousand.

This was, what about the rest of the errors? This was Lou Katz looking at his data, all right, given the original system in 2002, back to 2001, what should we do to improve it and how much benefit could we get out of it? You can see things like donor signatures missing, 20 percent of the errors there. The historian signatures missing was another 20 percent. The no-donor unit number, 25 percent, the incomplete physicals was -- what's that, 25 percent? The only one down that we can't get is insufficient documentation because that's a judgment call. But there's 15 percent we don't figure we'll ever get. The systems that we have, one we're releasing next month -- expect to be released in the next month -- should eliminate more than 90 percent of all the errors occurring from donor processing. We don't know for years, though, that we have.

This was one that was kind of odd, that we didn't really expect. This is post-donation information reports. And this was a small center, which is, some of us have to use twelve month ruling averages to get meaningful examples and it went down when we implemented, that center implemented in January 2005. And you can see initially you get the dip there but then it took off. And I talked to the woman that keeps these statistics yesterday to see if she could dig out some more data in another year and we'll see if we can come up with some better explanation. All we can think of or project on it is that we suspect it's due to the fact it triggers memory when people see the pictures and hear the audio and that adds more dimensions to the interview.

Summary, risky reporting is pretty similar prior to us implementing QDS but it becomes much more similar at the rate something like 10 or 11 per 1,000 post-implementation. The error reductions, this again, this is the first system back in early part of the century, got 61 to 67 percent reductions in the errors. There is also a staff time savings, which is substantial, comparable system, face-to-face interviewing, saves about five minutes; however, everybody uses different ways of interviewing the donors or there's a lot of variation in the ways and therefore to post something there and say it's a viable number is not, you know, we don't feel comfortable doing it. As I mentioned on the PDI reporting, we suspect it's due to the memory enhancement from the multimedia effect, and/or the increasing attention we get from the donors with the technology.

The conclusion, we believe, is that we have directly demonstrated an increase in transfusion safety but it is difficult or impossible to do it correctly because of the lack of any kind of testing data that takes donors that are deferred and says, figures out how many of them actually test positive for something.

We're taking what the technology does, is it reduces by very small amount the probability that an infected unit will pass through testing undetected. It also helps ensure human errors don't result into collection processing errors that may allow unsafe blood to enter the system, and the increased elicitation of critical donor histories which may be particularly important in blood safety where tests are not yet available for emerging threats to the blood supply.

A thing which is something we think, a couple of us at least in the group have been working on, this is very important is a public perception on this, that it tends to discourage the unsafe donors from donating while providing safe donors from the general public with overt evidence that the blood collection is making every effort to keep unsafe donors out of the system. Anyway, we have a Web site, there's data out here in the last four or five years to substantiate all this information. Thank you.

DR. BRACEY: Thank you for presenting. It appears to be a promising technology for a weak link that we've recognized. Questions or comments from the Committee? If not, I would like to move into the open discussion phase and for that we can pose questions.

One of the things as we pose the questions that I find

continually coming to my mind is the reason for the genesis of this Committee and that is the need to take action to prevent adverse outcomes related to transfusion. I mean, that is the history of this entity. And, another compelling thought is, as was mentioned earlier today by Dr. Roberts, in terms of the need to do the right thing, in a sense, and in my mind I think there's a fairly heavy weight toward pathogen reduction as perhaps the right thing to do, recognizing that there are unanswered questions.

So, at any rate, I would like to open it up to this phase for Committee discussion. And the first point is that understanding the advances and the challenges facing transfusion safety, what are the major safety concerns? And one point that was brought up in discussion, that perhaps Dr. Kuehnert would expand on this, is that we know what the current hazards are and they are quite low, in terms of viral

risk, of the key agents but the real concern would be
those things which we don't know that could evolve. Do
you want to talk a little bit more about that, Doctor?

DR. KUEHNERT: Sure. I can take a crack at it. I mean, I think we've heard a lot of very comprehensive presentations today and a lot of discussion about key agents and/or the agents of concern. And what that seems to mean are viral agents that have been much discussed over the last many years and that have been chiefly addressed, so much so that you have to model statistically to find out what the risk is because there are so few cases being reported. So, we keep on sort of looking at the same issues over and over and try to reduce that risk while there are these other risks that are obviously orders of magnitude higher but because of various barriers, when we discuss what those are, whether that be that there's no screening test or that we're not sure exactly, look at what morbidity and mortality is, in the recipients, it doesn't get as much attention. I just wonder, how do we, maybe we need to start by developing a paradigm for assessing what the risks are and then spending a proportionate amount of time on those rather than talking about the same threats over and over which have

chiefly already been addressed, at least for blood -- organ and tissue, maybe that's another matter -- but for blood, you know, we have to figure out exactly how to approach that.

DR. BRACEY: Dr. Kouides?

DR. KOUIDES: Yeah, Art, obviously earlier today there was a lot of emphasis about relative risks and concerns. We probably should prioritize the discussion also about relative safety concerns, mainly due to TRALI perhaps, you know, and I'm sure some of the discussion will be in there tomorrow about SD-plasma and the benefits of that in that sense but I'm wondering if we also want to, you know, prioritize the concerns.

DR. BRACEY: Yeah, that's a good idea. I

mean, clearly I think on one of the slides, well, on one of the slides that Dr. Dodd presented, that showed the relative risk, clearly TRALI, bacterial contamination these are the things that in the literature and in our experience have loomed as large continuing threats but I'll leave that up to the rest

of the Committee for discussion. Dr. Klein?

DR. KLEIN: Just one comment I want to make because it hasn't come up today and perhaps it should at least be said in passing, that arguably the largest risk is one that we haven't mentioned at all today, is really not a product but how the product is used, that is that blood is overtransfused, it's undertransfused, the wrong component is transfused. We all know this but it's something that perhaps is a little bit more difficult to deal with than adding an additional screening test or perhaps some of the other automated mechanisms of donor screening as were discussed.

DR. BRACEY: That's a good point. You know, actually, that did come up in some thoughts that

I had about this and what comes to mind is a clinical scenario. There are efforts now at blood conservation and those efforts, for example, in a case of something like a -- abdominal aneurysm repair, you can conserve a fair number of red cells so the predominant product used would be plasma and platelets. So, it really plays into the importance of the conservation piece in

terms of achieving, you know, the ultimate safety measure that you wish to do and if in fact, I mean, it's not a good thing to think of but if blood products are more expensive, then people will start looking more seriously at how they are utilized.

DR. KLEIN: If i might continue that for just one second. Even such a mindless concept as overtransfusion to the point where patients develop pulmonary edema, which we're increasingly seeing now that people are looking for it as a risk of transfusion, again it's on the practice side rather than the product component side, is something that I think need to be addressed.

DR. BRACEY: Good point. Dr. Triulzi?

DR. TRIULZI: Yeah, this is kind of a corollary related to it. It was said but I think the greatest threat, safety issue to the recipient is not having a sufficient supply of blood. I mean, that's something as I had the same experience Gerry did last week, that platelets supply was so low as to threaten the safety of, say, patient procedures. And, you know,

if you look at the curves between red cell availability and red cell distribution, they're almost overlapping now. There's that gap of 2, 3 percent. And, so, I would say that we don't have the excess blood any more to tolerate a test that's nonspecific and has a 1 percent or a half a percent deferral rate.

And, so, we can't continue with a strategy to add a test, even if we could over the next year every three months add a test for every one of those eight agents, we couldn't defer the 3 or 4 percent of donors or 5, or whatever it is, that are needed. We're already looking at TRALI, about taking the current platelet apheresis donors and cut 5 to 10 percent of those.

And, so, the testing strategy, whether we think it's the appropriate one or not, blood supply isn't going to allow us to do that. And I agree with everything that Harvey said. I think that the only appropriate forward-thinking solution is to change the strategy from reactive to proactive and just the savings in blood supply alone to me would go a long way

to justify that approach.

DR. BRACEY: Thank you. Ms. Finley?

MS. FINLEY: Thank you. This is the third time today I have heard some physicians say they didn't have platelets on the shelf when they needed them. I raised this issue repeatedly at our last two meetings. It's more of, you know, a hallway discussion but several people have approached me and mentioned it and I, you know, alerted people in HHS that I think I was hearing that there was a problem and generally if I hear about it, I assume that everybody else knows about it. I am uncomfortable about this, and I really would like the Committee to include the platelet issue if there is one or put it on, you know, in some way so that we get some assertation of exactly what's going on.

The second issue that I really think needs to be discussed is that we're not talking about a trade here for a test in terms of availability. The issue of availability is a collection issue and there are deferral issues that are associated with that. But to

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say that, you know, we're just blanket not going to consider a test because their potential impact is not accurate.

DR. BRACEY: No, I think that's a little bit out of context. We were talking about additional tests because the paradigm of testing, testing, testing, whenever there is a new agent, whenever you have the test, there's no such thing as a perfect test and you always have a number of false positives. So, what we experience are a number of people that in fact test positive on these screens and are therefore excluded and as you add more and more and more and more tests, you eliminate more and more and more individuals. So, if you had a system or a process whereby you could inactivate these agents and you did not need to do the assays, you wouldn't be at risk for losing people unnecessarily.

MS. FINLEY: Okay. I agree with the way you stated that. Are we getting ahead of ourselves here by making safety and efficacy pronouncements on technologies that are not yet reviewed by FDA?

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DR. BRACEY: Which technologies?

MS. FINLEY: Psoralen.

DR. BRACEY: Well, again we've heard from Dr. Epstein that in fact they have reviewed --

MS. FINLEY: The preclinical.

DR. BRACEY: The preclinical, yeah.

MS. FINLEY: They haven't reviewed the actual application.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: I think that Harvey Alter drew our attention properly to the issue, which is whether there was to be a commitment both by government, private sector, industry, to advance pathogen reduction as a priority goal. I don't think it's the purview of this Committee to make a safety and efficacy or effectiveness determination about pathogen reduction technology per se. First, you don't have the information, as has been pointed out and, you know, in the end that determination will lodge with the FDA. But larger framework is the goals and objectives of our blood system and, you know, if there's a commitment and

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if there's adequate funding and effort, I'm sure we can get there.

So, I know that it's easy to simply see the FDA regulatory processes as the current barrier but I think that the reality is that what we're trying to do is weigh a number of highly complex issues and the fundamental one is whether the cost of getting to a more precautionary strategy is justified given the current high level of safety of our blood system.

DR. BRACEY: Dr. Klein?

DR. KLEIN: I couldn't agree with you more, Jay, and I think we have really got the cart before the horse a little bit, because tomorrow we're going to hear all about these kinds of things. But in point OF fact, it's really not whether it's psoralen or Riboflavin or Inactine or really anything else. I think what we're really talking about right now is whether we should try to make a commitment to a new paradigm regardless of what the technology is.

And I think if you think about this for a second, this is a technological hurdle. It's not like

curing cancer, where it's so complex that there's no way in the world that you could say in three years we could do this. It's more like a Manhattan Project or like going to the moon, for example, where you really can see where you need to go but you're probably going to have put a lot of resource into getting there. In order to do that you really have to commit to sort of a different paradigm than the one we have had in the past.

MS. FINLEY : So, it's not unlike NAT, as was pointed out, the early days of NAT?

DR. KLEIN: I think in concept it's very much like NAT where people said you simply can't do this, it's too complex, you can't put this very sophisticated test into a very unsophisticated setting, a blood bank, until someone said, you know, we're going to do this. And then it can be done and I think, you know, regardless of what the technology is, pathogen reduction is not, more than rocket science but it's going to take a fair commitment resource to get there.

MS. FINLEY: So what we really need is a

question that doesn't, it doesn't start with NAT, it's more specific to the technological issues in pathogen reduction.

DR. BRACEY: Well, actually, I think the point that's being made is that this is a practical technology. What it represents is a move away from a tradition of simple processing of blood toward a higher technological method or approach to processing blood that's intended for transfusion with the end goal being that that component would be safer in terms of certain known -- there always will be unknown infections for which this has no value but there are a number of biological agents for which it would be very effective. I think Dr. Benjamin had a comment to make.

DR. BENJAMIN: Yes, I would just like to make a comment, too, that availability of the new technology should it come would provide opportunity to address the old problem. Two examples, TRALI being a good one, we know at least two of the available technologies, SD-plasma and the -- system that's used an additive solution both reduce the problem of TRALI, may not prevent it but reduce it.

The other one is availability. My understanding is that the French approach to pathogen inactivation where they were predominantly using apheresis platelets has been to cost-justify some of it by moving back to buffy coat platelets that are PI treated and that way you open up a whole availability of your resources -- that we don't use because there's a perceived extra risk of pooled products and, you know, manufacturer's treated system would be a major advantage to us to produce pooled platelets again.

DR. BRACEY: Well, the other availability issue that we're currently struggling with, for those of us in hospitals as we have moved towards TRALI, low-risk plasma, we've never had challenges with A-plasma before but currently we face that challenge and so this would clearly have an impact on that. And there is, I think, this a significant amount of concern by blood procurers as we move towards TRALI, risk reduction for platelets that could be a tremendous challenge and this would in essence eliminate that.

Ms. Benzinger?

MS. BENZINGER: I was just going to bring up something that seemed probably oversimplifying it but we are not addressing -- the part of the safety concern is the amount of supply. We never seem to be addressing how we increase the donor supply and what is our partnership in encouraging HHS to implement a program that is going to increase it based on donor supply. This is all part of the whole transplantation issue. In the time we're seeing it, there's a reason we had to prioritize who was a recipient of an organ an and who is the recipient of the blood supply that's in a limited amount had to do something to address the fact there are plenty of donors out here. Are we approaching all of those donors? And again I understand the whole idea that you're talking about all the safety concerns but again if you increase that supply.

DR. BRACEY: Yeah, one of the things that we have endorsed and the agency is responding to, is to start at the point of having the data and that is what we discussed at our August meeting. We need to know what the numbers are. We, you know, we hear, you know, anecdotal reports of shortages and there are shortages that are reported in the system -- robust system and that's one of things that we're trying to foster.

DR. KUEHNERT: I think, yeah, part of the problem is that we don't have a good way right now to evaluate availability and safety, either one, and it makes everyone quite uncomfortable. We're sort of saying, well, we try things and then say we think it worked but we're not sure. If there were a system to look at both those issues we would feel a lot better, you know, if we had data that's more than anecdotal.

The other thing is there's sort of this tradition of when an intervention gets put in that's it. I mean, it's stuck there. I mean syphilis testing, that's a good example, when we're talking about removing syphilis testing forever. So, this is what I'm talking about as far as the paradigm. It's not only about pathogen reduction. It's about evaluating each and every risk and each and every intervention and if we're thinking we're not going to be able to remove any, say, screening measure, then it's going to be very difficult to, you know, argue that some huge investment in, say, pathogen reduction is going to somehow be a major shift and say, the cost of blood, or it's going to reduce the cost of blood or it's going to change availability because you're just going to have the same test in place. But you have to be able, we have to be able to I think evaluate any of these to be able to make a major change in the way the system is working.

DR. BRACEY: Well, one comment made that Dr. Alter had posed is important and that is there are some assays that we currently have questions about the efficacy and so there are few that we perhaps could see going away. There are certain ones that, you know, are unlikely to go away, HIV, et cetera.

DR. KUEHNERT: Yeah, but I'm not hearing there's any chance that can happen. I don't see how that could happen. From my standpoint -- maybe I just don't understand but I don't see how there's a way that

that could happen and maybe that's restricting my ability to see the benefits of other approaches, so.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: Yeah, I just wanted to cite some facts and figures. You know, one way of looking at the question of what our priorities should be is look at what causes fatalities and FDA, as you know, gathers data on both donor related and recipient related fatalities from a mandatory reporting system. And for cumulative data for '05 and '06, TRALI is now about 50 percent of all fatalities reports. Now, of course there's an ascertainment that there's more awareness of TRALI, but certainly it highlights the importance of TRALI. About a quarter of all fatalities are related to hemolytic transfusion reactions. Most of those are non-APO. The figures are 20 percent of fatalities are APO and 7 percent non-APO, that part, hemolysis. Microbial infection is about 10 to 12 percent. It's been consistent over many years and it's almost exclusively bacterial.

We know there are, you know, rare cases of

malaria, babesia, but it's virtually all bacterial contamination. And then interestingly transfusion and associated circulatory overload is a reported cause of fatality, accounting for about 7 percent of all those transfusion-attributable tests. So, you know, I think that this gives us a little bit of a quantitative sense about where the problems lie and, you know, very much conforms with what people have been saying around the table about the bigger picture. And, but I guess, you know, within the framework of this meeting, we have been pretty much focused on the issue of infectious risks. And, you know, there I think that we had a very good summary obviously by Roger but, you know, sort of the highlights that I took away are that the biggest risk is bacterial infection. Then the second to that we have the issue of focality, in other words, for example, babesia risk may be as high as one per thousand in confined geographical areas.

The Chagas story is really similar to that.

The available data suggests a general national exposure risk of about 1 in 30,000 putting aside for the moment

the question of risk of transmission, which is, you know, under study. But then there are areas of the country where the exposure risk absent screening would have been much higher, around, you know, for example, 1 in 4 to 8,000 in Florida and California. And then I think what then jumps out after that we have a question mark about hepatitis B because the residual risk estimates coming out of the window period incidence model don't seem to reconcile with actual reports right now.

And then we have the issue of EIDs, which is really what's driving the discussion about pathogen reduction; that's about preparedness. And I think that, you know, we do have a national commitment to preparedness. We just haven't been thinking in the same way about preparedness against disasters and preparedness against EIDs. So, it's part of preparedness and we have been investing in preparedness. So, that's just my effort to put a few of the threads together.

DR. BRACEY: Thank you. Dr. Ramsey?

DR. RAMSEY: Thanks, I got a couple of items, I guess we haven't heard about yet, maybe we will more tomorrow, and that this is the cost of these measures. We heard of the presentations about the market and the business side of this, in past discussions, we heard about problems of reimbursement and, you know, the overall effect on cost. So, although that's not the primary, our primary purpose it would be helpful to have some idea of the costs of these procedures.

The other thought that occurred to me is that we haven't heard yet about the reliability of these measures of pathogen reduction, in other words, does it work as well, will it work as well on the mass scale as it might in smaller batches, so to speak, particularly if it's going to be applied to pooled products, whether it be a large number of donors in there. So, but even for single-unit products, what would be the reliability of this system and, i.e., or, you know, the implications of how much of our older procedures do we need to still rely on as far as the

potential problem?

DR. BRACEY: I think clearly tomorrow we will have an opportunity to hear more about much of this role of modified plasma, TRALI and certainly opportunity to ask direct questions regarding cost and failures and also we should hear on surveillance related to the use of these products. Dr. Klein?

DR. KLEIN: I'd just like to leave a couple of thoughts in the heads of the Committee members who don't think about this all the time, because we are going to hear a lot more about this tomorrow. The first thought that I would like to leave is that I hope that the Committee isn't going to be trying to decide as to whose manufacturer's pathogen reduction we ought to endorse or not endorse because I don't think that is the Committee's job -- as Jay suggested, that's the FDA's job -- but programs whether or not we should think of a new paradigm.

And related to that a thought I would like to leave you with is so-called EIDs, which were for those of you who don't know, is emerging infectious

diseases. If you think about what's happened in this country since World War II, we've seen reliably every 10 to 15 years a new emerging infectious disease. That's caused an enormous amount of problem in this country in terms of morbidity and mortality as well as a lack of public confidence in the blood supply. These aren't really new agents; they're old agents. Even retroviruses are around forever but perhaps a mutation in a virus makes it literally inevitable that this is going to happen again.

It may be something mild, like West Nile, which again was a mutation that probably caused the problem or something a lot less mild, like HIV, which if it entered the blood supply last week, we would not know about that until several years from now and those who receive plasma fractions would be just fine and those who receive blood components that are not plasma fractions would be in big trouble. And that will happen again. You can model what the costs and benefits might be, what the risks and benefits and costs and benefits might be by looking at what happened

with HIV, for which we have a lot of data and what happened with West Nile virus, or what might happen in between. So, I think we need to think about these things when we think about the current paradigm that we have and maybe where we ought to go in this century.

DR. BRACEY: Another thing that I thought that was very important was the second model of risk that was presented by Dr. Chapman because in fact we accept a certain degree of risk by labeling these products as, quote, biologicals, but, if there's something that we can do to minimize that biological risk, again, that puts paradigm, taking as much, as many steps as we can down the road towards making these components safe because there are individuals who are affected by these challenges. Dr. Holmberg?

DR. HOLMBERG: Just to sum up what I've heard, I've heard a lot about paradigm and in just hearing what people have said around the table here, one paradigm that I have heard is that we need to be proactive and not reactive, that we need to evaluate the risk, there should be a systematic review of newly

introduced mitigation, the paradigm of availability and paradigm of utilization.

DR. KUEHNERT: Yeah, I would just add not only newly introduced mitigation but anciently introduced mitigation as well because I think they're both important.

DR. BRACEY: Another thing is one of the questions addresses the barriers, and, you know, it's odd when you think -- and Dr. Sandler has been good for reminding us of this -- that in 1998 or so, whenever

SD-plasma was available there was no barrier. It did come to market. It was available. So, you know, we can't really say well, you know, the FDA stopped us from using these products. If there were problems associated with those products, then what comes to mind is if we think these products are safe and effective and we know that -- and this is a huge, a larger problem but -- and we know that these products are available in other parts of the world, then why would we not consider using products that might be derived somewhere else? In other words, I know it raises a big

issue but if there are safer products that are, quote, importable, than could we import them? Dr. Epstein?

DR. EPSTEIN: Well, products subject to regulation must meet U.S. standards for U.S. distribution. That's not to say that the FDA cannot review non-U.S. data. We can review non-U.S. data but a product sponsor that wishes to distribute a product must bring those data to the FDA.

DR. BRACEY: Right. Right. But, because I think tomorrow, for example, we will hear about Octaplas, but what I don't know -- and there are people here who are anticipating in the trial -- Octaplas is a source that's derived in the U.S or what is the source of the donors?

DR. RAMSEY: Well, the trial I think most of us are referring to is Uniplas, which is a new product for the company, or newer product for the company, but, I don't want to say for sure what the origin of the product is.

DR. MALTAS: U.S., U.S.

DR. RAMSEY: It is U.S., all U.S.

DR. BRACEY: Okay, okay. Initial comments? If there are no other comments, I think we're at a pretty good time for adjournment. We'll meet -- what time do we start tomorrow? Nine o'clock, 9 a.m. tomorrow.

(Meeting suspended at 6:00 p.m.)

State of Maryland.
Baltimore County, to wit:

I, ROBERT A. SHOCKET, a Notary Public of the State of Maryland, County of Baltimore, do hereby certify that the within-named proceedings personally took place before me at the time and place herein set out.

I further certify that the examination was recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor in any way interested in the outcome of this action.

As witness my hand and notarial seal this 22nd day of January, 2008.

____

Robert A. Shocket,

Notary Public

My Commission Expires:
November 1, 2010